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ORIGINAL ARTICLE

Efficacy and safety of nilotinib in Japanese patients with imatinib-resistant or -intolerant Ph+ CML or relapsed/refractory Ph+ ALL: a 36-month analysis of a phase I and II study

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Abstract Although the tyrosine kinase inhibitor (TKI) imatinib is often used as first-line therapy for newly diagnosed chronic myelogenous leukemia (CML), some patients fail to respond, or become intolerant to imatinib. Nilotinib is a potent and selective second-generation TKI, with confirmed efficacy and tolerability in patients with imatinib-resistant or -intolerant CML. A phase I/II study was conducted in Japanese patients with imatinib-resistant or -intolerant CML or relapsed/refractory Ph+ acute lymphoblastic leukemia. Thirty-four patients were treated with nilotinib for up to 36 months. Major cytogenetic response was achieved in 15/16 patients (93.8%) with chronic-phase CML within a median of approximately 3 months. Major molecular response was achieved in 13/16 patients (81.3%). These responses were sustained at the time of the most recent evaluation in 13 patients and 11 patients, respectively. Hematologic and cytogenetic responses were also observed in patients with advanced CML. The BCR-ABL mutation associated with the most resistance to available TKIs, T315I, was observed in three patients. Common adverse events included rash, nasopharyngitis, leukopenia, neutropenia, thrombocytopenia, nausea, headache and vomiting. Most adverse events resolved following nilotinib dose interruptions/reductions. These results support the favorable long-term efficacy and tolerability of nilotinib in Japanese patients with imatinib-resistant or -intolerant chronic-phase chronic myeloid leukemia.

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Introduction

The tyrosine kinase inhibitor (TKI) imatinib (ST1571, Glivec™; Novartis) has been shown to induce durable responses in a high proportion of patients with chronic-phase chronic myeloid leukemia (CML-CP) [1–5]. However, disease progression caused by resistance to imatinib occurs in some CML patients treated with this drug [6].

CML patients in the accelerated phase (CML-AP) or in blast crisis (CML-BC) also show a complete cytogenetic response (CCyR) following treatment with imatinib, but the proportion of such patients achieving CCyR is considerably lower than that of CML-CP patients [7, 8]. Moreover, imatinib resistance and relapse are also common in CML-AP and -BC patients [6, 9]. Imatinib is also used to treat patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL), and many of these patients also achieve CCyR. However, the CCyRs in these patients are not sustained for as long as they are in CML-CP patients, both in Japan [10] and in other countries [11].

Approximately half of the cases of imatinib resistance are now known to result from mutations in *BCR-ABL* [12–16], which make particular leukemic cells resistant to BCR-ABL tyrosine kinase inhibition by imatinib.

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Nilotinib (AMN107, Tasigna®; Novartis) is a second-generation TKI that inhibits BCR-ABL-dependent cell proliferation and induces cell death in BCR-ABL phenotypic cells [17, 18]. Nilotinib was originally approved as second-line treatment for imatinib-resistant or -intolerant CML-CP and -AP patients [19–22]. More recently, it was approved as first-line therapy for CML-CP and -AP patients [23, 24] in Japan. Several studies have reported hematologic response (HR) and cytogenetic response (CyR) with nilotinib in patients with imatinib-resistant or -intolerant CML-BC and those with relapsed/refractory Ph+ ALL [25, 26].

We recently reported the results of a phase I and II study of nilotinib in which Japanese patients with imatinib-resistant or -intolerant Ph+ CML, or relapsed/refractory Ph+ ALL were treated for up to 12 months [22]. Here, we report the effects of treatment with nilotinib for up to 36 months in these patients, as well as the results of mutation analysis and the response by BCR-ABL mutation status.

Materials and methods

Study design and objectives

This was an open-label, multicenter, continuous-dose, 36-month extension of a phase I and II clinical study. The study protocol and documentation were approved by the institutional review boards of each participating center. The observation period was defined to be 36 months, including the entire 3 months of the Ph I/II clinical study. The study was conducted in accordance with the ethical principles established by the Declaration of Helsinki and in compliance with institutional guidelines.

The primary objective of this extension study was to evaluate the long-term safety of nilotinib, including chronic toxicity. Secondary objectives included the long-term efficacy of nilotinib, the relationship between BCR-ABL mutations or BCR-ABL transcript levels determined by quantitative RT-PCR, and the clinical efficacy of nilotinib. The time of last evaluation in this study was the time at which patients had received treatment for more than 3 years or the time at which the drug became commercially available at each of the study institutions, whichever was the later.

Patients

The inclusion and exclusion criteria are described in the original study report [22]. Briefly, Japanese patients were eligible if they had imatinib-resistant or -intolerant CML-CP, CML-AP, CML-BC or relapsed/refractory Ph+ ALL, were at least 20 years of age, had a World Health Organization (WHO) performance status (PS) ≤ 2, and had normal hepatic, renal and cardiac function.

Treatments

Nilotinib 400 mg was administered orally twice daily. Patients were required to fast for 2 h before and after each dose. One treatment course (1 cycle) was defined as 28 consecutive days of twice-daily nilotinib. If administration was delayed for more than 21 days (42 days for hematologic toxicity) after the previous dose, the patient was withdrawn from the study. Dose reductions to 400 mg once daily (one level lower than the standard dose) or 200 mg once daily (two levels lower than the standard dose) were permitted. The nilotinib dose at re-introduction was one level lower than that at cessation. The mean dose in each patient was calculated by assuming the dose during the cessation period to be 0 mg.

Treatment with nilotinib was continued until disease progression or unacceptable toxicity was observed, or at the investigator's discretion that treatment be discontinued. After the regulatory approval date for nilotinib in Japan (January 29, 2009), its administration was continued for longer than 3 years or until the drug became commercially available, whichever was later.

Measurements

Response rates

Criteria for HR and CyR were similar to those reported elsewhere [19, 21, 27] and are described in more detail in Tojo et al. [22]. Briefly, CyR was determined as the percentage of Ph+ cells of ≥20 cells in the metaphase in each bone marrow sample, and was classified as complete (0% Ph+ cells), partial (1–35% Ph+ cells), minor (36–65% Ph + cells) or minimal (66–95% Ph+ cells). Major CyR (MCyR) included complete and partial CyR. Fluorescent in situ hybridization was used if <20 cells were examined or if the bone marrow sample was not adequate for assessment.

The proportion of patients who experienced major molecular response (MMR) was also determined for each disease phase and subtype. BCR-ABL transcript levels were measured by quantitative RT-PCR and reported in the international scale using a conversion factor of 1.25 established by the Institute of Medical and Veterinary Science, Australia. MMR was defined as a BCR-ABL/BCR ratio ≤0.1%. Loss of MMR was defined as a BCR-ABL/BCR ratio >0.1%. Patients with MMR at baseline were considered "not evaluable" and were excluded from the analysis. Only evaluable patients in the intention-to-treat (ITT) population were included in the analyses of overall response rates.

Patients whose BCR-ABL transcript levels were not evaluated at baseline were considered "not assessable", and were not included in the denominator when calculating the proportion of patients who achieved MMR.

Mutation analysis

Efficacy was also examined based on the subtype of BCR-ABL mutation at baseline and after nilotinib administration. Mutation analysis was performed by the direct sequence identification method. The number and proportion of patients with HR, CyR or MMR were calculated for the following categories of mutation [22]: no mutation, any mutation, multiple mutations, P-loop mutations (amino acids 248–255), non-P-loop mutations, and protocol-specified subgroup mutations associated with imatinib resistance mutations (L248, Q252, T315, F317, H396, M237, M244, G250, D325, S348, M351, E355, A380, L387, M388, F486, Y253, E255, and F359). The impact of baseline mutations or development of new mutations on patient outcomes was assessed.

Safety analyses

Safety assessment included an evaluation of the frequency and severity of adverse events, which included hematologic and biochemical laboratory tests, vital signs, physical examinations (including body weight), WHO PS, cardiac function tests (12-lead ECG, cardiac enzyme test, echocardiography), and chest X-rays, as needed. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). The monitoring was continued for at least 28 days after the last dose of nilotinib.

Statistical analyses

The ITT population was used for the efficacy analysis and was pre-specified as all patients enrolled in either the phase I or phase II studies, and who were treated with nilotinib 400 mg twice daily, irrespective of when they withdrew from the study. The safety (SAF) population comprised all patients in the ITT population who underwent safety assessments. HR, CyR and MMR were summarized by disease phase and subtype (CML-CP, CML-AP, CML-BC, and Ph+ ALL). The time to first response and duration of response were assessed by descriptive statistics or Kaplan–Meier analysis, as appropriate. No statistical comparisons were made.

Results

Patients and treatment administration

This 36-month study included 34 Japanese patients with imatinib-resistant or -intolerant CML (CML-CP, $N = 16$; CML-AP, $N = 7$; CML-BC, $N = 4$) or Ph+ ALL ($N = 7$).

Thirty-one patients were enrolled into the phase II study and treated with nilotinib 400 mg twice daily (CML-CP: 14, CML-AP: 7, CML-BC: 3; Ph+ ALL: 7) and 3 patients were enrolled in the phase I study and treated with nilotinib 400 mg twice daily (CML-CP: 2; CML-BC: 1) [22]. The characteristics and disposition of patients are summarized in Tables 1 and 2, respectively. Fourteen patients (CML-CP: 13; CML-AP: 1) received nilotinib until the end of the study while 20 patients (CML-CP: 3, CML-AP: 6, CML-BC: 4; Ph+ ALL: 7) discontinued study treatment. The

Table 1 Patient characteristics (ITT population)

	CML-CP ($N = 16$)	CML-AP ($N = 7$)	CML-BC ($N = 4$)	Ph+ ALL ($N = 7$)	Total ($N = 34$)
Age (years)	57.0 (30–83)	61.0 (30–74)	53.0 (29–70)	62.0 (23–80)	61.5 (23–83)
Sex					
Male	9 (56)	5 (71)	2 (50)	6 (86)	22 (65)
Female	7 (44)	2 (29)	2 (50)	1 (14)	12 (35)
Body weight (kg)	61.2 (44.5–89.0)	64.8 (49.1–83.0)	63.3 (35.5–69.0)	55.8 (46.2–60.2)	60.5 (35.5–89.0)
WHO PS					
0	16 (100)	4 (57)	2 (50)	4 (57)	26 (76)
1	0 (0)	2 (29)	2 (50)	3 (43)	7 (21)
2	0 (0)	1 (14)	0 (0)	0 (0)	1 (3)
Time since first diagnosis (months)	30.4 (1.4–122.8)	108.6 (12.5–192.8)	65.3 (20.5–102.8)	16.2 (3.7–134.1)	30.4 (1.4–192.8)
Imatinib resistance	4 (25.0)	4 (57.1)	4 (100.0)	7 (100.0)	19 (55.9)
Imatinib intolerance	12 (75.0)	3 (42.9)	0 (0.0)	0 (0.0)	15 (44.1)
Highest imatinib dose (mg)	500 (200–800)	800 (400–800)	700 (600–800)	600 (600–600)	600 (200–800)

Values are *n* (%) or median (range)

ITT intention-to-treat, *WHO PS* World Health Organization performance status

Table 2 Patient disposition (ITT population)

	CML-CP ($N = 16$)	CML-AP ($N = 7$)	CML-BC ($N = 4$)	Ph+ ALL ($N = 7$)	Total ($N = 34$)
Completed the long-term study	13 (81)	1 (14)	0 (0)	0 (0)	14 (41)
Discontinued treatment and withdrawn from the study	3 (19)	6 (86)	4 (100)	7 (100)	20 (59)
Reason for discontinuation					
Adverse event(s)	0 (0)	1 (14)	1 (25)	1 (14)	3 (9)
Allo-HSCT performed	1 (6)	2 (29)	1 (25)	0 (0)	4 (12)
Disease progression	1 (6)	3 (43)	2 (50)	6 (86)	12 (35)
Withdrawal of consent	1 (6)	0 (0)	0 (0)	0 (0)	1 (3)
Dose reduction	15 (94)	5 (71)	3 (75)	4 (57)	27 (79)
Withdrawal from treatment	11 (69)	2 (29)	2 (50)	2 (29)	17 (50)
Drug administration recommenced at a reduced dose after withdrawal	10 (63)	1 (14)	0 (0)	2 (29)	13 (38)
Duration of exposure (days)[a]	1099.5 (176–1173)	84.0 (56–1099)	133.0 (15–247)	56.0 (13–644)	445.5 (13–1173)
Duration of administration (days)[b]	1084.5 (165–1173)	84.0 (28–1099)	126.5 (14–247)	56.0 (13–609)	428.0 (13–1173)
Daily dose (mg)[c]	612.9 (394.2–798.6)	789.6 (284.9–797.5)	742.6 (402.4–798.4)	785.7 (483.2–794.1)	750.7 (284.9–798.6)

Values are *n* (%) or median (range)

Allo-HSCT allogeneic hematopoietic stem cell transplantation, *ITT* intention-to-treat

[a] Includes drug interruptions

[b] Excludes drug interruptions

[c] Daily dose = total dose/duration of exposure (includes drug interruption)

Table 3 Best responses to nilotinib (ITT population)

	CML-CP ($N = 16$)	CML-AP ($N = 7$)	CML-BC ($N = 4$)	Ph+ ALL ($N = 7$)
Hematologic response (HR)	6 (100)[a]	5 (71)	2 (50)	3 (43)
Complete hematologic response	6 (100)	1 (14)	1 (25)	–
Complete response	–	–	–	3 (43)
Marrow response with no evidence of leukemia	–	3 (43)	0 (0)	–
Return to chronic phase	–	1 (14)	1 (25)	–
Stable disease	0 (0)	1 (14)	2 (50)	1 (14)
Progressive disease	0 (0)	0 (0)	0 (0)	3 (43)
Not evaluable/not assessable	10 (63)	1 (14)	0 (0)	0 (0)
Cytogenetic response (CyR)				
Major	15 (94)	1 (14)	2 (50)	–
Complete	13 (81)	1 (14)	2 (50)	–
Partial	2 (13)	0 (0)	0 (0)	–
Minor	0 (0)	0 (0)	1 (25)	–
Minimal	1 (6)	3 (43)	0 (0)	–
None	0 (0)	1 (14)	0 (0)	–
Not assessable	0 (0)	2 (29)	1 (25)	–
Molecular response (MR)				
Major[b]	13 (81)	1 (14)	2 (50)	1 (17)[c]
None	3 (19)	6 (86)	2 (50)	5 (83)[c]
Not evaluable	0 (0)	0 (0)	0 (0)	1 (14)

Values are *n* (%)

[a] Of which 6 were evaluable

[b] Major molecular response was defined as a BCR-ABL/BCR ratio ≤0.1%

[c] Of which 6 were evaluable

ITT intention-to-treat

most frequent reason for discontinuation was disease progression in 12 patients. Disease progression was seen in 1 patient with CML-CP, 3 patients with CML-AP, 2 patients with CML-BC and 6 patients with Ph+ ALL.

The median duration (range) of nilotinib exposure was 445.5 days (13–1173 days) and that of administration was 428.0 days (13–1173 days). The median daily dose (range) of nilotinib was 750.7 mg/day (284.9–798.6 mg/day) in all patients, consistent with the planned dose of administration (400 mg twice daily = 800 mg/day) in the study protocol. Dose reductions occurred in 27 patients (79.4%) because of adverse events in 19 patients (55.9%), in accordance with the study protocol in 14 patients (41.2%), incorrect administration in 10 patients (29.4%) or incorrect scheduling in 1 patient (2.9%) (multiple dose reductions were possible). Treatment interruption occurred in 17 patients (50.0%) because of adverse events in all 17 patients. Thirteen of these patients showed improvement of adverse events and were able to restart nilotinib administration at a lower dose.

Efficacy

CML-CP

The best responses (HR, CyR and MR) in the ITT population are shown in Table 3. All 6 CML-CP patients without CHR at baseline achieved CHR. The median time

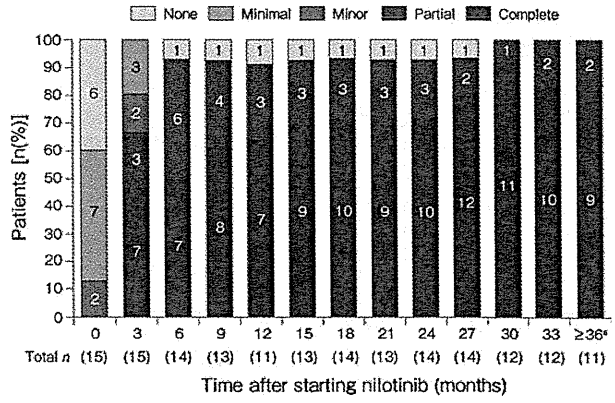

Fig. 1 Cytogenetic responses in CML-CP patients. [a]Including up to and beyond 36 months

(range) to CHR was 28 days (28–56 days). Of these, 5 patients showed sustained response up to the last evaluation, while the remaining patient discontinued treatment on Day 787 because of disease progression. The duration of CHR in that patient was 478 days. MCyR was achieved in 15 patients (93.8%) and the response was sustained at the last evaluation in 13 patients. CCyR was achieved in 13 patients (81.3%) and the response was sustained at the last evaluation in 11 patients. The median time (range) to MCyR or CCyR was 84 days (28–178 days) and 97 days (57–847 days), respectively. The rate of CyR in evaluable patients at each time point is shown in Fig. 1. Thirteen

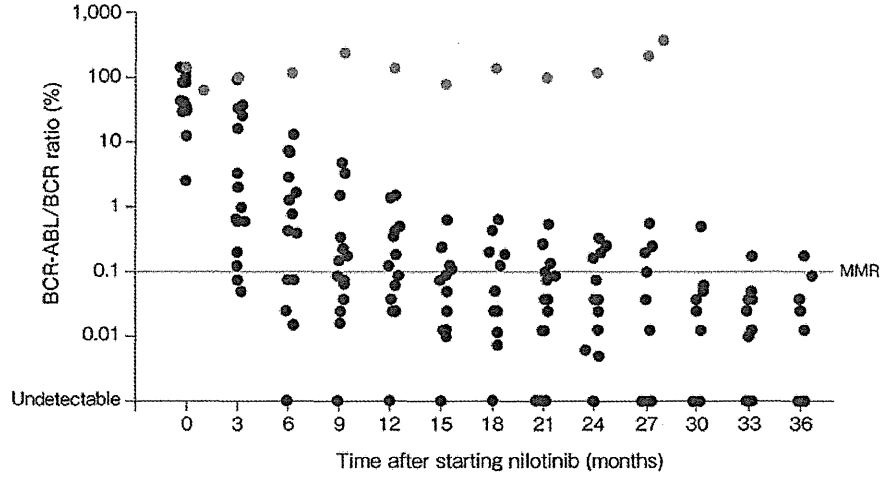

Fig. 2 Molecular responses during the 36-month study in patients with CML-CP. *MMR* major molecular response

patients continued treatment at 36 months or later. Among them, 11 patients were evaluated as showing cytogenetic response, all of whom achieved MCyR, including 9 with CCyR. The figure shows that the proportion of CCyRs increased with nilotinib treatment period.

The BCR-ABL/BCR ratio in CML-CP patients over time is shown in Fig. 2. The BCR-ABL/BCR ratio gradually decreased from baseline with long-term nilotinib treatment in all patients except one with baseline or newly detected mutations. An approximately 1-log reduction in BCR-ABL/BCR ratio from baseline at 6 months and an approximately 2-log reduction at 12 months were observed. MMR was achieved in 13 patients (81.3%) and was sustained at the last evaluation in 11 patients. The median time (range) to MMR was 248 days (84–852 days) in these CML-CP patients.

Among CML-CP patients, 3 patients discontinued nilotinib treatment. One patient discontinued treatment on Day 176 to undergo allogeneic hematopoietic stem cell transplantation (allo-HSCT). Another patient once achieved CCyR but discontinued treatment on Day 787 because of disease progression, as mentioned above. This patient had a newly detected mutation (F359V). Another patient withdrew consent on Day 931.

CML-AP

Among 7 CML-AP patients, 5 patients (71.4%) achieved HR, including CHR in 1 patient, marrow response with no evidence of leukemia in 3 patients, and return to chronic phase in 1 patient. Of the remaining 2 patients, 1 had stable disease and 1 was not evaluable. Of the 5 patients with HR, 1 patient with CHR and another 2 patients with HR experienced sustained response at the last evaluation or at discontinuation of treatment. In the remaining 2 patients, the duration of HR was 29 and 57 days, respectively. Minimal CyR was observed in 3 patients (42.9%). One patient with CHR achieved CCyR (14.3%). This patient also achieved MMR, which was sustained at the last evaluation.

CML-BC

Among 4 CML-BC patients, 2 patients (50.0%) achieved HR, including CHR in 1 patient and return to chronic phase in 1 patient. They also achieved CCyR and MMR. In both patients, MCyR was sustained until discontinuation of treatment to undergo allo-HSCT (on Day 247) in the first patient, or because of increasing blast numbers in bone marrow (on Day 168) in the second patient. The remaining 2 patients (50.0%) experienced stable disease and one of them achieved minor CyR.

Ph+ ALL

Among 7 patients with relapsed/refractory Ph + ALL, 1 of 5 patients (20.0%) without MRD experienced HR (complete response [CR]), which was sustained for 108 days. Three patients experienced disease progression and 1 experienced stable disease. Both patients with MRD achieved HR (CR). In one of these patients, CR was sustained for 58 days, but treatment was discontinued on Day 109 because of encephalitis. In the other patient, CR was sustained for 470 days, but treatment was discontinued on Day 644 because of disease progression. MMR was achieved in 1 patient with MRD, while the other patient with MRD achieved MMR at baseline and was thus considered not evaluable.

BCR-ABL mutations

Detection of new mutations

The development of new BCR-ABL mutations during the administration of nilotinib in this study is shown in

Table 4 Detection of new BCR-ABL mutations

Stage	Mutation	Day of detection	Baseline mutation	Achieved MMR	Outcome
CML-CP	F359V	174	M244V	No	Disease progression
CML-CP	E255K	340	None	Yes	Continued
CML-BC	T315I/Y253H	168	F317L	Yes	Disease progression
Ph+ ALL	T315I	16	E255K/E255V/G250E	No	Disease progression
Ph+ ALL	E255V	57	E459K	No	Disease progression
Ph+ ALL	T315I	43	None	No	Disease progression
Ph+ ALL	E255K/E255V	135	NA	No	Disease progression

MMR major molecular response, *NA* Not assessable

Table 4. New mutations were detected in 7 patients during nilotinib treatment. Among them, the T315I mutation occurred in 3 patients and nilotinib was discontinued in these patients because of disease progression. Three of the 4 patients with mutations other than T315I also discontinued treatment because of disease progression. The remaining patient continued treatment.

CML-CP

Among 16 CML-CP patients, MMR was observed in 4 of 5 patients (80.0%) with BCR-ABL mutations at baseline or emerging during the treatment period. As shown in Table 4, new mutations were detected in 2 patients.

One patient had a baseline M244V mutation and achieved minimal CyR on Day 87; however, an F359V mutation was also detected on Day 174. From Day 426, only the F359V mutation was detected and the M244V mutation was not; this patient was withdrawn from the study because of disease progression on Day 787 (see "CML-CP" under the heading Efficacy). In another patient without baseline mutation, E255K was detected only once on Day 340. This patient achieved MMR on Day 511, which was sustained at the last evaluation, and the mutation was not detected again after achievement of MMR. In 1 patient with an imatinib resistance-associated mutation (F359I) at baseline, the mutation could not be detected after commencing nilotinib treatment, which led to MMR that had been sustained for 666 days at the last evaluation.

CML-AP/-BC and Ph+ ALL

Among 7 CML-AP patients, no new mutations were detected. As shown in Table 4, among 4 CML-BC patients, new mutations were detected in 1 patient with the F317L mutation at baseline. This patient achieved CCyR and MMR on Day 56; however, Y253H and T315I mutations were detected on Day 168 followed by disease progression on Day 171. Among 7 Ph+ ALL patients, new mutations were detected in 4 patients, all of whom experienced disease progression.

Safety analysis

All adverse events regardless of drug relationship occurring at a frequency ≥20% and those of grade 3/4 are summarized in Table 5 (adverse events and adverse drug reactions occurring in ≥10% of subjects are shown in Supplemental Tables 1 and 2, respectively, while all adverse events of grade 3 or worse are shown in Supplemental Table 3). Adverse events occurred in all of the patients. The most common non-hematologic events were rash (64.7%), nasopharyngitis (58.8%), nausea and headache (47.1% each), and vomiting (41.2%). Hematologic events included leukopenia (47.1%), neutropenia (47.1%), thrombocytopenia (47.1%) and anemia (38.2%).

Adverse events of grade 3/4 occurred in 29/34 patients (85.3%). The most frequent grade 3/4 non-hematologic events were abnormal hepatic function, hyponatremia and pneumonia (11.8% each). Grade 3/4 hematologic events included neutropenia (47.1%), leukopenia (41.2%), thrombocytopenia (32.4%), anemia (29.4%) and lymphopenia (11.8%). The most common biochemical grade 3/4 events were decreased blood phosphorus levels (14.7%), hyperglycemia and increased lipase levels (11.8% each).

Serious adverse events

Thirty-four serious adverse events occurred in 19 patients. Among these, 21 events in 12 patients were considered possibly related to nilotinib. Two of these patients discontinued nilotinib treatment because of serious adverse events considered to be related to the drug. One, with CML-BC, developed back pain (non-serious) and discontinued treatment. Two days later, this patient developed cardiac tamponade and pericardial effusion, and died because of heart failure. The other, with Ph+ ALL, developed encephalitis and also discontinued treatment. Furthermore, one CML-CP patient developed acute pancreatitis reported as a serious adverse event that resolved

Table 5 Non-hematologic, hematologic and biochemical adverse events with a frequency ≥20% for all grades

Total $N = 34$	All grades					Grade 3/4				
	CML-CP *n* (%)	CML-AP *n* (%)	CML-BC *n* (%)	Ph+ ALL *n* (%)	Total *n* (%)	CML-CP *n* (%)	CML-AP *n* (%)	CML-BC *n* (%)	Ph+ ALL *n* (%)	Total *n* (%)
Non-hematologic events										
Rash	9 (56.3)	5 (71.4)	3 (75.0)	5 (71.4)	22 (64.7)	1 (6.3)	0 (0.0)	1 (25.0)	0 (0.0)	2 (5.9)
Nasopharyngitis	15 (93.8)	3 (42.9)	2 (50.0)	0 (0.0)	20 (58.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	7 (43.8)	2 (28.6)	3 (75.0)	4 (57.1)	16 (47.1)	0 (0.0)	0 (0.0)	1 (25.0)	1 (14.3)	2 (5.9)
Nausea	6 (37.5)	3 (42.9)	4 (100.0)	3 (42.9)	16 (47.1)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (2.9)
Vomiting	6 (37.5)	3 (42.9)	2 (50.0)	3 (42.9)	14 (41.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	4 (25.0)	1 (14.3)	4 (100.0)	4 (57.1)	13 (38.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	8 (50.0)	2 (28.6)	1 (25.0)	1 (14.3)	12 (35.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperbilirubinemia	5 (31.3)	3 (42.9)	1 (25.0)	1 (14.3)	10 (29.4)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.9)
Hyperglycemia	8 (50.0)	1 (14.3)	1 (25.0)	0 (0.0)	10 (29.4)	2 (12.5)	1 (14.3)	1 (25.0)	0 (0.0)	4 (11.8)
Malaise	8 (50.0)	0 (0.0)	0 (0.0)	2 (28.6)	10 (29.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	6 (37.5)	0 (0.0)	2 (50.0)	1 (14.3)	9 (26.5)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (2.9)
Pruritus	3 (18.8)	2 (28.6)	1 (25.0)	3 (42.9)	9 (26.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal hepatic function	5 (31.3)	0 (0.0)	1 (25.0)	2 (28.6)	8 (23.5)	1 (6.3)	0 (0.0)	1 (25.0)	2 (28.6)	4 (11.8)
Conjunctivitis	7 (43.8)	1 (14.3)	0 (0.0)	0 (0.0)	8 (23.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	3 (18.8)	2 (28.6)	1 (25.0)	2 (28.6)	8 (23.5)	0 (0.0)	0 (0.0)	1 (25.0)	1 (14.3)	2 (5.9)
Anorexia	5 (31.3)	1 (14.3)	0 (0.0)	1 (14.3)	7 (20.6)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Arthralgia	5 (31.3)	2 (28.6)	0 (0.0)	0 (0.0)	7 (20.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eczema	6 (37.5)	0 (0.0)	1 (25.0)	0 (0.0)	7 (20.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypokalemia	1 (6.3)	2 (28.6)	2 (50.0)	2 (28.6)	7 (20.6)	0 (0.0)	1 (14.3)	0 (0.0)	1 (14.3)	2 (5.9)
Insomnia	2 (12.5)	2 (28.6)	1 (25.0)	2 (28.6)	7 (20.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngitis	4 (25.0)	0 (0.0)	0 (0.0)	3 (42.9)	7 (20.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hematologic events										
Leukopenia	7 (43.8)	3 (42.9)	2 (50.0)	4 (57.1)	16 (47.1)	5 (31.3)	3 (42.9)	2 (50.0)	4 (57.1)	14 (41.2)
Neutropenia	7 (43.8)	3 (42.9)	2 (50.0)	4 (57.1)	16 (47.1)	7 (43.8)	3 (42.9)	2 (50.0)	4 (57.1)	16 (47.1)
Thrombocytopenia	7 (43.8)	3 (42.9)	2 (50.0)	4 (57.1)	16 (47.1)	3 (18.8)	3 (42.9)	2 (50.0)	3 (42.9)	11 (32.4)
Anemia	5 (31.3)	2 (28.6)	3 (75.0)	3 (42.9)	13 (38.2)	3 (18.8)	2 (28.6)	2 (50.0)	3 (42.9)	10 (29.4)
Biochemical events										
Increased bilirubin	6 (37.5)	1 (14.3)	1 (25.0)	2 (28.6)	10 (29.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Increased alanine aminotransferase	3 (18.8)	0 (0.0)	2 (50.0)	3 (42.9)	8 (23.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	1 (2.9)
Increased lipase	5 (31.3)	1 (14.3)	1 (25.0)	1 (14.3)	8 (23.5)	3 (18.8)	1 (14.3)	0 (0.0)	0 (0.0)	4 (11.8)

The table includes drug-related and non-related adverse events combined

following nilotinib dose interruption. This patient restarted nilotinib at 400 mg once daily, which was then increased to 400 mg twice daily, and the subject completed study treatment. QT interval prolongation occurred in 1 CML-CP patient and nilotinib treatment was interrupted. This patient restarted nilotinib at 400 mg once daily and continued treatment without QT interval prolongation.

Adverse events by time-points

Among the CML-CP patients, the incidences of blood/lymphatic system disorders, gastrointestinal disorders, laboratory abnormalities, and skin/subcutaneous tissue disorders in Cycles 1–12 in the first year of treatment were 68.8, 87.5, 62.5 and 75.0%, respectively. The incidences of these events were much lower during Cycles 13–24 (20.0, 40.0, 40.0 and 53.3%, respectively) and Cycles 25 or later (20.0, 73.3, 26.7, 46.7%) in the second year of treatment. Gastrointestinal disorders showed higher incidence in Cycles 25 or later (3 years or more of treatment) and, in particular, the incidence of constipation was as high as 26.7%. Fewer patients with CML-AP, CML-BC, and Ph+ ALL continued treatment beyond Cycle 24, so no significant difference in the

incidence of these adverse events between time-points was observed.

Discussion

Here, we report the long-term efficacy and tolerability profiles of nilotinib in 34 patients with imatinib-resistant or -intolerant Ph+ CML or relapsed/refractory Ph+ ALL. In comparison with the findings obtained at 12 months [22], there were few occurrences of new adverse events during the 36-month study.

In the phase I/II clinical trial of nilotinib [22], the drug was found to be generally safe and well-tolerated in patients with imatinib-resistant or -intolerant CML, and those with relapsed/refractory Ph+ ALL. The tolerability of nilotinib up to doses of 400 mg twice daily was confirmed in Japanese patients. The dose intensity of nilotinib increased with increasing dose within the investigated dose range, and the 400 mg twice-daily dose regimen gave the highest exposure.

In the present extension study, in CML-CP patients, CCyR was achieved in 13/16 patients (81.3%) and CCyR was achieved rapidly, within a median of approximately 3 months. Furthermore, MMR (defined as a BCR-ABL/BCR ratio $\leq$0.1%) was also achieved in 13/16 patients (81.3%). These results compare favorably with those reported after 24 months of nilotinib treatment in another study of imatinib-resistant or -intolerant CML-CP [20]. In that study, 44% (141/321) of patients achieved CCyR and 28% (82/294) of patients achieved MMR. Comparable rates of HR, CyR and MMR during nilotinib therapy in CML-CP were reported in other studies. In this analysis, 13/16 patients achieved MMR and, in some patients, the BCR-ABL transcript level was undetectable by quantitative RT-PCR.

One CML-AP patient who responded well to nilotinib and achieved CCyR was treated with nilotinib for 3 years. This suggests that nilotinib has long-term benefits for the treatment of some patients with CML-AP. The findings in Ph+ ALL and CML-BC patients in this study are similar to those reported in other studies [26]. Although the sample size is small, the results obtained in 4 CML-BC patients and 7 Ph+ ALL patients suggest that, in some patients, nilotinib may be an effective drug for the treatment of imatinib-resistant or -intolerant CML-BC and Ph+ ALL. Further studies are needed in patients with advanced CML to verify these results. All 5 Ph+ ALL patients without MRD in this study were previously treated with imatinib, and only 1 patient (20.0%) achieved HR. The other 4 patients ultimately discontinued treatment because of disease progression. In contrast, both Ph+ ALL patients with MRD achieved HR. The small sample size in this study meant that patients with imatinib-resistant or -intolerant disease were considered together, not separately.

As reported previously [28], imatinib resistance or intolerance, or the presence of baseline BCR-ABL mutations associated with imatinib resistance, did not affect the response to nilotinib. We detected 5 new mutations in 7 patients after starting nilotinib treatment. T315I, which is the mutation associated with the most resistance to currently available TKIs, was detected in 3 patients (8.8%) with CML-BC or Ph+ ALL; these patients discontinued treatment because of disease progression. Three of the 4 patients who developed other mutations also discontinued treatment, and the remaining patient, who had an E255K mutation, achieved MMR. These findings are consistent with previous studies suggesting that patients with the T315I mutation have a poor response to nilotinib [12, 19].

Two types of amino acid substitution at F359, F359V and F359I, were detected in this study. A CML-CP patient with baseline M244V mutation later harbored an F359V mutation (detected on Day 174) and showed poor response to nilotinib treatment; this patient experienced disease progression, as seen in other patients with the F359V mutation described in previous reports [29]. On the other hand, another patient who had F359I mutation at baseline achieved MMR. A previous study [30] showed that the F359I mutation is moderately sensitive to nilotinib (IC_{90} value = 433 nM). Nevertheless, in the present study, nilotinib treatment was effective, and sustainable MMR was observed in the patient with F359I mutation at baseline.

A recent study also described that CML patients with baseline mutations on imatinib treatment were more likely to relapse because of the development of other mutations after receiving dasatinib or nilotinib as second-line treatment [31]. Although the sample size of our study was small, only one CML-CP patient with a BCR-ABL mutation showed disease progression while the others completed study treatment. The effects of BCR-ABL mutation on the efficacy of treatment may differ depending on not only the type of mutation, but also the disease type and stage.

Adverse events of any grade occurred in all of the patients, regardless of drug relationship, and adverse events of grade 3/4 occurred in 29/34 patients (85.3%). The most common hematologic or non-hematologic adverse events included rash, nasopharyngitis, nausea, headache, vomiting, leukopenia, neutropenia and thrombocytopenia. Hematologic adverse events were commonly of grade 3/4 severity, similar to previously reported findings [19–21, 25, 26, 28]. Abnormal biochemical findings included hyperbilirubinemia, hyperglycemia and increased lipase. The rates of abnormal hematologic/blood biochemical findings were similar to those reported in a 12-month study [22] and in a global phase II study [19–21]. Most of these events

were not serious. The majority of adverse events did not require treatment discontinuation, interruption or dose reduction. Taken together, these findings are comparable with those reported in global phase I and II clinical studies [19–21, 25, 26] and a retrospective multicenter analysis [28]. During the 36-month observation period, only one patient with CML-BC died. Death resulted from heart failure due to cardiac tamponade and pericardial effusion occurring after discontinuation of nilotinib treatment.

Hematological and cytogenetic effects of nilotinib have been already observed in studies of up to 12 months [22] or 24 months in duration [20]. We have extended these findings in Japanese patients with imatinib-resistant or -intolerant Ph+ CML (CP, AP, or BC) or relapsed/refractory Ph+ ALL treated with nilotinib 400 mg twice daily for up to 36 months in this study. Importantly, nilotinib was shown to be effective as a second-line treatment for patients who failed to respond to previous imatinib treatment and who were considered to have a poor prognosis, with many patients achieving HR and CyR, which were maintained until last observation. No safety concerns arose over 36 months of treatment that were not apparent during the first 12 months of treatment. Most adverse events resolved following nilotinib dose interruption, dose reduction or supportive care.

The median daily dose of nilotinib (750.7 mg; range 284.9–798.6 mg) was below the prescribed dose (800 mg), mainly as a result of dose reductions in response to adverse events. In a previous study of nilotinib in Japanese newly diagnosed CML patients [24], the median dose was 730 mg (range, 644–794 mg) in the group administered nilotinib 400 mg twice daily; this dose was not considered particularly low, providing dose intensities similar to those in the overall population. The dose reduction in that study [24] was similar to that in ours.

Nilotinib was approved in Japan for the treatment of patients with CML-CP or CML-AP, but not patients with CML-BC or Ph+ ALL. The results of this study update provide further evidence supporting the use of nilotinib in Japanese patients with CML-CP or CML-AP. Our results also suggest that nilotinib may be useful for the treatment of patients with CML-BC or Ph+ ALL. Indeed, efficacy was observed in some CML-BC and Ph+ ALL patients; however, it remains to elucidate for which patient populations this drug would be most suitable in CML-BC and Ph+ ALL.

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Conflict of interest Taro Amagasaki and Aira Wanajo are employees of Novartis Pharmaceuticals. The other authors have no conflicts of interest to disclose.

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Late effect of Atomic bomb radiation on myeloid disorders: leukemia and myelodysplastic syndromes

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Abstract Leukemia was the first malignancy linked to radiation exposure in atomic bomb survivors. Clear evidence of the dose-dependent excess risk of three major types of leukemia (acute lymphocytic leukemia, acute myeloid leukemia [AML], and chronic myeloid leukemia) was found, especially in people exposed at young ages. Such leukemia risks were at their highest in the late 1950s, and declined gradually thereafter over the past 50 years. Findings from recent risk analyses, however, suggest the persistence of AML risk even after 1990, and evidence of increased risk of myelodysplastic syndromes (MDS) due to atomic bomb radiation has recently been shown. High-risk MDS and forms involving complex chromosomal aberrations were found to be much more frequent in people exposed to higher radiation doses. These lines of epidemiological evidence suggest that the risk of radiation-induced hematological malignancies has persisted for six decades since the initial exposure.

Keywords Atomic bomb survivors · Ionizing radiation · Leukemia · Myelodysplastic syndromes · Genomic instability

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Introduction

Ionizing radiation is a well-established human carcinogen. Numerous population studies have clearly showed the association between the higher-dose radiation and the higher incidence of various malignancies. The effects of ionizing radiation on human body can be separated into two phases: "early effects" such as acute radiation syndrome, and "late effects" that occurred latter following acute phase. One of the major problems of the "late effects" is the long-lasting effect on the development of malignancies.

Much of what we have known about the long-term carcinogenic effects of radiation exposure comes from studies of Hiroshima and Nagasaki atomic bomb survivors. Nearly 3 years after the atomic bombings in 1945, local doctors in Hiroshima and Nagasaki for the first time noticed the increased number of patients with leukemia in survivors. This early observations led to the establishment of a multidisciplinary collaborative project named "Open City Study (OCS)" in 1950, which was a population-based leukemia registry system including other hematological malignancies in both cities. The first epidemiological paper reporting a clear evidence of an excess risk of leukemia in survivors was published in 1952 [1]. Then, in 1958, a cohort of Life Span Study (LSS) in the Radiation Effects Research Foundation (RERF) was established to investigate the long-term effects of radiation exposure on the development of all malignancies by linkage of Nagasaki and Hiroshima tumor registries. The LSS cohort included about 120,000 people, of whom about 93,000 were in Hiroshima or Nagasaki City at the time of bombing. With OCS and LSS studies, cases of leukemia were captured well in both cities. Now these systems grew larger by linked to the regional tumor registries of both cities, and

cases with a variety of malignant diseases have been accumulated. Since then, considerable scientific evidence has published for over 60 years in collaboration with a variety of investigators, including epidemiologists and statisticians at RERF, and pathologists and hematologists at Hiroshima and Nagasaki universities.

As mentioned above, leukemia was the first malignancy to be associated with radiation exposure in atomic bomb survivors. The incidence of leukemia began to increase rapidly in the early 1950s and declined gradually, whereas the incidence of solid cancers began to increase in the early 1970s and have been still increasing. The excess risk of leukemia due to radiation exposure was the extremely highest among various malignancies in atomic bomb survivors. Therefore, leukemia is considered as a predominant type of radiation-induced malignancies in this population. Moreover, recent our work showed the clear dose–response increase in the incidence of myelodysplastic syndromes (MDS), a leukemia-related hematological malignancy, among Nagasaki survivors even after 40 years from exposure, suggesting that the risk of hematological diseases would last life-long. Based on these epidemiological evidence, this review would like to focus on hematopoietic late effects of radiation observed in Hiroshima and Nagasaki survivors.

Leukemia

Overview

The earliest reports of a dose–response increased risk of leukemia in the LSS cohort of atomic bomb survivors was published in 1971 and 1978 [2, 3]. These reports also showed that for the first time there was a significant relationship between the risk of leukemia and age at bombing and time from the exposure. Since then, a series of reports regarding the risk of leukemia was published until the early 1980s. Although the dose–response risk was tried to analyze separately by acute granulocytic leukemia, acute lymphocytic leukemia, and chronic granulocytic leukemia, the type of leukemia in those days was based on the classic classification, which was not exactly identical for modern leukemia classification.

In 1976, a new morphological classification of leukemia, especially of acute leukemia, was established by the French-American-British (FAB) group [4]. It was immediately used world-wide, and could be applied for leukemia diagnosed among survivors between 1950 and 1980, which were 339 cases in the LSS cohort and 766 cases in the OCS cohort. In the mid-1980s, three hematologists reclassified over 60% of the cases of leukemia using the FAB classification [5, 6].

In the LSS cohort, 180 cases were reclassified among 193 cases of leukemia available for peripheral blood smear and/or bone marrow smear [5]. Of those, there were 17 cases with acute lymphoblastic leukemia (ALL), 88 cases of acute myeloid leukemia (AML), 18 cases of chronic myeloid leukemia (CML), and only 3 cases of chronic lymphocytic leukemia (CLL). Because Adult T-cell leukemia/lymphoma (ATL) had already recognized as a distinct disease entity caused by human T-cell-leukemia virus type-1 (HTLV-1) in the middle 1970s in Japan, 30 cases of ATL was also reclassified. Most of the ATL cases among survivors were found in Nagasaki, and it later showed that there was no relationship between radiation dose and the risk of ATL. As well known, Nagasaki City is located in the western part of the island of Kyushu is one of the endemic area of HTLV-1 infection.

In the OCS cohort, 493 cases were reclassified based on the FAB classification into 66 (13.4%) of ALL, 195 (39.9%) of AML, 110 (22.4%) of CML, 4 (0.8%) of CLL, and 42 (8.6%) of ATL. Moreover, in AML, a variety of subtype was determined; M1, a myeloblastic type without maturation of leukemia cells, M2 with maturation of leukemia cells, M3 of promyelocytic, M4 and M5 with the involvement of monocytic lineage, M6 of erythroleukemia, and M7, a megakaryoblastic type. The number of each subtype is shown in Table 1 [6]. So far, there is no data to show whether or not there is any difference in the frequency of subtypes of AML between atomic bomb survivors and general population. Adjuvant radiation therapy for patients with malignancies may increase the development of secondary leukemia or therapy-related leukemia, however, the distribution of FAB subtypes is identical between therapy-related leukemia and leukemia in atomic bomb survivors. There is a report to show that AML patients who were exposed more than 1 Gy of atomic bomb radiation had heavily complex karyotype in AML cells [7]. Therefore, karyotypic analysis of AML would help to solve the issue above, although there was no karyotypic technique until 1960s.

Table 1 FAB subtype of AML among survivors (data from reference [5])

FAB subtype	Number of cases (%)
M1	20 (24.7)
M2	24 (29.6)
M3	13 (16)
M4	10 (12.4)
M5	7 (8.6)
M6	6 (7.4)
M7	1 (1.2)
Total	81

Based on the re-classification of leukemia using FAB criteria, dose–response and time-dependent trend were performed for four major subtypes of leukemia. Tomonaga et al. [6] analyzed the leukemia subtype data reclassified cases for the period from 1945 to 1980 in the OCS cohort in 1993, suggesting that relative risks for ALL and CML are greater than those for AML and that there is no evidence of an excess risk for ATL or CLL. This analysis also gave an important information on a difference in the risk with by subtypes of leukemia, suggesting that ALL and CML rise and reached the peak in the excess risk rapidly after exposure and then declines, whereas the peak in the excess risk of AML occurred later than ALL and CML. Preston and Tomonaga et al. [8] analyzed the leukemia subtype data reclassified cases for the period from 1950 to 1987 in the LSS cohort in 1994. In this report, 237 cases of leukemia with estimated dose by DS86 were used to calculate excess absolute risk (EAR) and excess relative risk (ERR), considering the effect of age at exposure, gender, time after exposure (attained age). EAR was described as excess the number of leukemia patient per 10,000 person-year per Sv. ERR is expressed as relative risk (RR) minus one described as relative risk per Sv when the risk of minimally exposed cases was set as 1. Since the 1994 report is the latest analysis for the incidence of leukemia in atomic bomb survivors, we summarize this report below.

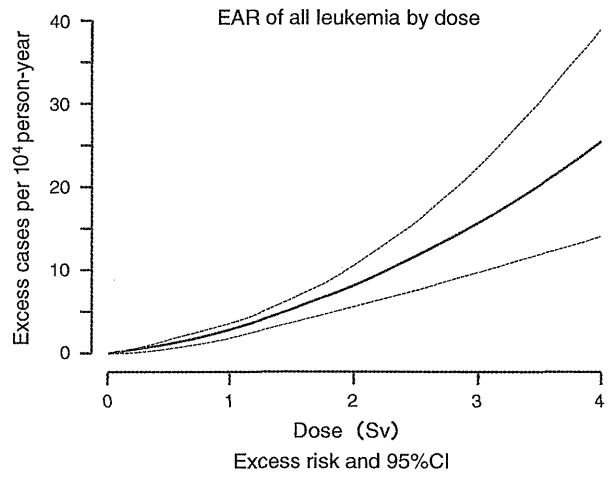

Fig. 1 EAR of all leukemia by dose. The relationship between radiation dose and the excess absolute risk of whole leukemia is shown. *Solid line* is the fitted curve, and the *dotted lines* show the 95% confidence interval (data from reference [8])

Dose–response risk of whole leukemia

If all types of leukemia cases are combined, there is a statistically significant dose response (Fig. 1, $P < 0.001$), which seems non-linear. The dose–response curve is convex downward. The risk itself decreased along with time after exposure. EAR of all types of leukemia was significantly related with gender, age at exposure, and attained age (Fig. 2). Young male had high EARs in the period from 5 to 10 years after exposure, and old men did not have as high risk as young. However, the risk declines more slowly than young. The risk for women was generally lower than men, but that for older female did not seem to decline along with time, suggesting that it may not be so simple as risk of leukemia goes away after certain duration. A model of leukemia risk fitted better when age at exposure and an interaction between age at exposure and time are considered. Adding the interaction of sex and time also gave a better fit for the model than sex alone as a factor. With this model, risk for women decreased slowly with time than for men. The EAR did not differ by city. These results showed that the risk of leukemia differs by sex, age at exposure, attained age, and dose, suggesting a complex mechanism of leukemogenesis by radiation.

Dose–response risk of leukemia by subtype

In this study, risk of leukemia was tested by major subtypes of leukemia: ALL, AML, CML, and CLL. However,

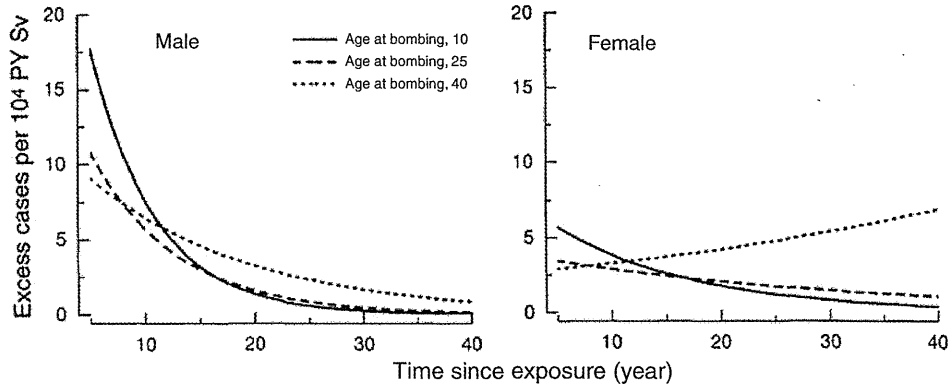

Fig. 2 EAR of all types of leukemia by gender, age at exposure, and attained age. The effect of sex and age at exposure for EAR of whole leukemia is shown. These are estimated using a fitted model that was exposed at 1 Gy. *Left* male, and *right* figure for female (data from reference [8])

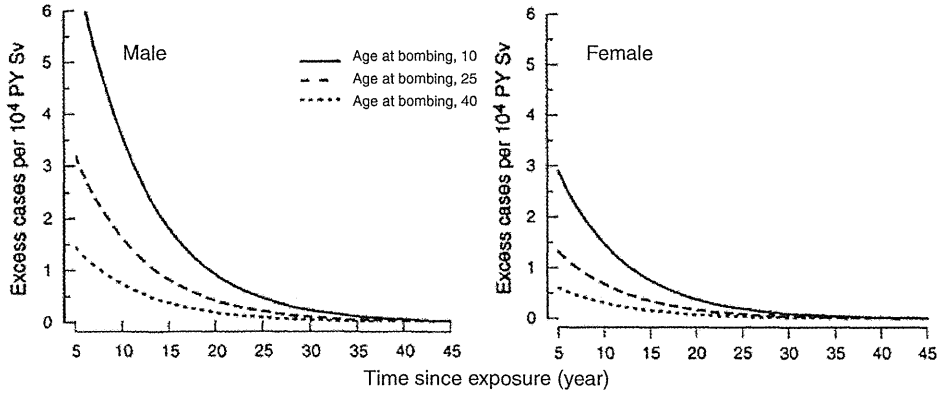

Fig. 3 EAR of ALL by gender, age at exposure, and attained age. EAR of ALL that was affected by sex, age at exposure, and time since exposure is shown. These curves are fitted model for those received 1 Gy. *Left panel* for male, and *right panel* for female (data from reference [8])

because of the small number of CLL cases, risk was not examined well for CLL.

ALL

A dose response of ALL risk was highly significant ($P < 0.001$). Using a linear response model, the EAR decreased with time since exposure and the time-average EAR decreased with increasing age at exposure. Children exposed under age 10 had the highest excess risk, and old female had the lowest risk. Figure 3 demonstrated the EAR for male and female that exposed 1 Sv at the ages of 10, 25 and 40 years. The model-based risk estimates the EAR as 0.62 per 10^4 person-year.

AML

There was a strongly significant dose–response between risk of AML and radiation ($P < 0.001$), which was not a linear pattern. Age at exposure had significant effect on EAR with younger survivors had higher average EAR. Contrast to ALL, sex did not have a significant effect on EAR for AML. Although the EAR for the young decreased along with time, those more than 20-year-old showed constant or increasing risk with time, which also differed from ALL (Fig. 4). Because of the number of cases, risk of each FAB subtype was not tested.

CML

For the EAR for CML, a linear dose–response pattern fitted well. The background rate of CML was significantly different between two cities. Hiroshima male had the highest back ground, and Nagasaki female had the lowest background rate. The EAR for CML decreased rapidly with time. Although age at exposure did not influence the risk,

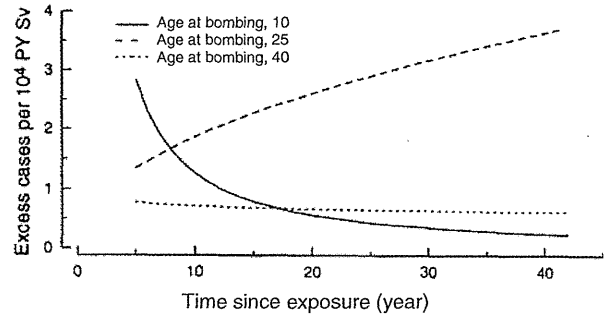

Fig. 4 EAR of AML by age at exposure and attained age. EAR of AML by age at exposure and attained age is shown (models that received 1 Gy). There is no significant effect of sex for EAR of AML, which is different from for ALL (data from reference [8])

there was a significant difference between the EARs for Hiroshima and Nagasaki ($P = 0.005$). The magnitude of the city effect seemed to be explained by differences of the background rates in both cities.

Other leukemias

ATL did not show dose–response, and it is confirmed that radiation exposure did not increase the risk of viral induced leukemia/lymphoma by HTLV-1. The number of CLL cases was too small to analyze.

Leukemia risk after 1990

The results above were based on the data until 1987. So far in three major subtypes of leukemia, ALL, AML and CML, EARs roughly decreased along with time. It seems that the decrease will also continue after 1990, and that it will be soon at the background level or it had been. Although the analyses using an extended follow-up period are in progress, the mortality of leukemia was calculated using LSS data until 2000 [9]. In this report, AML showed a distinct

pattern than other leukemias such as ALL and CML. From 1950 to 2000, there were 124 cases of AML-related death, 58 of CML-related and 19 of ALL-related death with dosimetry system 02 (DS02) dose estimation. ERRs of mortality at 1 Gy were 2.81 for AML, 6.39 for CML and 3.70 for ALL. The ERRs showed clear increase around 10 years after exposure, then decreased rapidly, however, when AML analyzed separately, it showed clear increase after 55 years from exposure (Fig. 5). We do not know what it means so far, but the incidence analysis will be very important, especially for AML. Such effort is under progress.

Myelodysplastic syndromes (MDS)

MDS was clearly defined by FAB group in 1982 [10]. Although several groups of hematologists had already noticed diseases called refractory anemia that did not respond to general treatment, or hematological disorder that proceeded acute leukemia, MDS was not recognized well. It took for a while to be recognized as neoplasm widely. Even "Tumor registry" did not deal MDS as neoplasm until WHO classification defined MDS as neoplasm. These situations had made it very difficult to collect epidemiological data for MDS.

It is well known that chemotherapeutic agents such as alkylating agents can cause MDS and leukemia (mostly AML). These are called therapy-related MDS (AML) or secondary MDS (AML) that are thought to be different from de novo cases. As mentioned above, radiation is a causative agent for leukemia. However, so far, it has not been clear whether radiation causes MDS or not. In the same article describing leukemia among atomic bomb survivors (published in 1994 Ref. [8]), 2 cases of MDS were included, which were too small in number to analyze the relationship between radiation and MDS. To elucidate the relationship between atomic bomb and MDS, "Open City cohort" cases and the LSS cohort were evaluated in Nagasaki area [11]. Among 64,058 survivors who were alive in 1985, 151 cases of MDS were confirmed in the Nagasaki "Open City cohort" (NOC) from 1985 to 2004. These cases had an information about the exposure distance from the hypocenter. In the LSS cohort, among those who were alive at 1985 (22,245 cases), 44 cases of MDS were diagnosed by 2004. These cases had estimated bone marrow dose (DS02). As shown in Tables 2 and 3, each data base provided MDS cases in the category by distance (Table 2, NOC) or bone marrow dose (Table 3, LSS cohort). For MDS cases in NOC, the median age at exposure was 18.5 years (range 0.3–43.4 years), and the

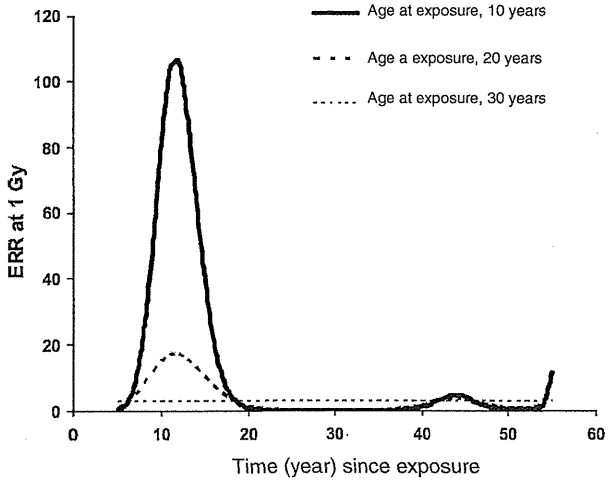

Fig. 5 ERR of mortality by AML at 1 Gy by age at exposure. The excess relative risk of mortality by AML is shown. *Y* axis shows the time after exposure (data from reference [9])

Table 2 MDS cases in the Nagasaki "Open cohort" (data from reference [11])

Exposure distance from the hypocenter (km)	<1.5	1.5–2.999	>3	Total
Sex				
Male	1,693	6,485	16,092	24,270
Female	2,258	10,663	26,835	39,756
Total	3,951	17,148	42,927	64,026
MDS FAB subtypes				
RA	15	28	57	100
RARS	0	1	3	4
RAEB	7	8	14	29
RAEB-t	2	2	2	6
CMML	1	3	4	8
Unclassified	0	2	2	4
Total	25	44	82	151

Table 3 MDS cases in the LSS cohort (data from reference [11])

Bone marrow dose by DS02 (Gy)	>= 1	0.005–0.999	<0.005	Total
Sex				
Male	273	2,665	5,904	8,842
Female	351	4,201	8,851	13,403
Total	624	6,866	14,755	22,245
MDS FAB subtypes				
RA	5	9	20	34
RARS	0	1	0	1
RAEB	2	3	2	7
RAEB-t	1	2	0	3
CMML	0	0	0	0
Unclassified	0	0	2	2
Total	8	15	24	47

Table 4 Crude rate and crude relative risk of MDS in Nagasaki "Open cohort" and LSS cohort (data from reference [11])

Exposure distance from the hypocenter (km)	<1.5	1.5–2.999	>3	Total
Crude rate	43.1	17.6	12.8	15.9
Crude relative risk	3.2	1.4	Reference	
Bone marrow dose by DS02 (Gy)	≥1	0.005–0.999	<0.005	Total
Crude rate	80.7	26.6	10.5	17.4
Crude relative risk	8.1	1.4	Reference	

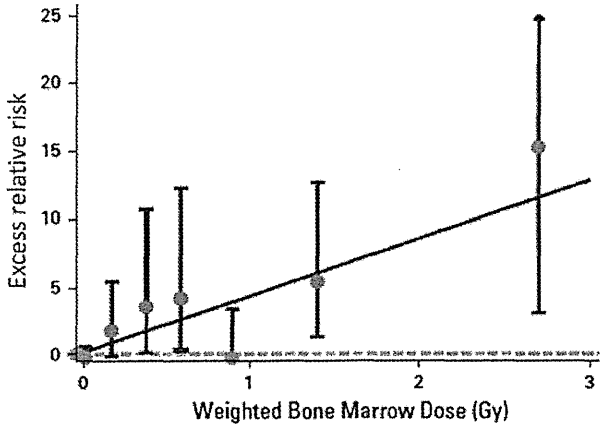

Fig. 6 Fitted relationship between excess relative risk of MDS and bone marrow dose. *Solid line* shows the relative risk of MDS by dose, and *dotted line* for control (data from reference [11])

median age at diagnosis were 71.0 years (range 42.0–96.6 years). For MDS in LSS, those were 16.5 years (range 2.5–48.8 years) and 72.4 years (range 48.5–94.3 years), respectively. Using these data, crude incidence and crude relative risk of MDS were analyzed in each category. The crude MDS incidence rates in the NOC and LSS cohort were 15.9 and 17.4 patients per 100,000 person-year, respectively (Table 4). MDS rates were higher for men than for women and increased with age at exposure as total. MDS rates also increased with decreasing distance from the hypocenter in both Nagasaki and LSS cohort, and with increasing estimated dose in the LSS cohort.

When sex and age at exposure were adjusted, Cox analysis showed that the MDS incidence rate was significantly and inversely related to the exposure distance in the NOC. 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- and low-risk MDS in both cohorts (Fig 2a, b). Through these analyses, it was suggested that the dose of radiation and distance from the hypocenter had stronger effects on high-risk MDS than low-risk MDS. In terms of the effect of age at exposure, when we adjusted for attained age in 1985 in the NOC, age-specific MDS risks was higher in the young age group; with risks for those born after 1925 is about 1.75 (95% CI, 1.05–2.90) times as those born in earlier years. The fitted distance-response curve is shown in Fig. 6. It was a linear relationship (ERR 4.3 at 1 Gy).

Hematological disorders as long-term effects of atomic bomb radiation

In the analyses using "Open City cohort" of Hiroshima and Nagasaki, and the LSS cohort, it is clear that radiation by atomic bomb caused several hematological neoplasms as late effects. The increase of leukemia was noticed some years after exposure and it was evident at least 5 years after exposure. Dose had a significant relationship with the risk of leukemia and MDS, clearly demonstrating that radiation is a causative factor for both leukemia and MDS. However, considering the effects of sex, age at exposure, and attained age on the risks for these diseases, there would be very complex biological mechanisms of how hematological neoplasms develop after radiation exposure.

The risk of MDS increased at least 45 years after exposure, and also the relative risk of AML mortality. These data raise the suggestion that the risk of hematological neoplasms could be lifelong for survivors. So far, there is no clear explanation how the effect of atomic bomb lasts for such a long period. Considering the hierarchy of hematopoiesis, it is assumed that only hematopoietic stem cells could hold the effects of radiation for such a long time, however, this hypothesis needs to be examined. Epidemiological data from "Open City cohort" of Hiroshima and Nagasaki, and the LSS cohort have been providing pivotal data of the effects of radiation on human, which will and has very important sources. Because the possibility of the life-long risk for hematological neoplasms among survivors, which was suggested by recent works, highlighted the necessity of the continuing follow-up of both cohorts.

Conflict of interest None.

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Impact of graft-versus-host disease on outcomes after allogeneic hematopoietic cell transplantation for adult T-cell leukemia: a retrospective cohort study

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Impact of graft-versus-host disease on outcomes after allogeneic hematopoietic cell transplantation for adult T-cell leukemia: a retrospective cohort study

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Allogeneic hematopoietic cell transplantation (HCT) is an effective treatment for adult T-cell leukemia (ATL), raising the question about the role of graft-versus-leukemia effect against ATL. In this study, we retrospectively analyzed the effects of acute and chronic graft-versus-host disease (GVHD) on overall survival, disease-associated mortality, and treatment-related mortality among 294 ATL patients who received allogeneic HCT and survived at least 30 days posttransplant with sustained engraftment. Multivariate analyses treating the occurrence of GVHD as a time-varying covariate demonstrated that the development of grade 1-2 acute GVHD was significantly associated with higher overall survival (hazard ratio [HR] for death, 0.65; $P = .018$) compared with the absence of acute GVHD. Occurrence of either grade 1-2 or grade 3-4 acute GVHD was associated with lower disease-associated mortality compared with the absence of acute GVHD, whereas grade 3-4 acute GVHD was associated with a higher risk for treatment-related mortality (HR, 3.50; $P < .001$). The development of extensive chronic GVHD was associated with higher treatment-related mortality (HR, 2.75; $P = .006$) compared with the absence of chronic GVHD. Collectively, these results indicate that the development of mild-to-moderate acute GVHD confers a lower risk of disease progression and a beneficial influence on survival of allografted patients with ATL. (*Blood.* 2012;119(9):2141-2148)

Introduction

Adult T-cell leukemia (ATL) is a mature T-cell neoplasm that is causally associated with a retrovirus designated human T-cell leukemia virus type I (HTLV-I).[1-4] HTLV-I is endemic in southwestern Japan, sub-Saharan Africa, the Caribbean Basin, and South America.[3,4] In Japan, more than 1 million people were estimated to be infected with HTLV-I. Although the majority of HTLV-I–infected individuals remain asymptomatic throughout their lives, ~ 5% develop ATL at a median age of 40 to 60 years.[4,5]

ATL is categorized into 4 clinical variants according to its clinical features: smoldering, chronic, acute, and lymphoma types.[6] The acute and lymphoma variants of ATL have an extremely poor prognosis, mainly because of resistance to a variety of cytotoxic agents and susceptibility to opportunistic infections; the median survival time is ~ 13 months with conventional chemotherapy,[7,8] although encouraging results have been recently reported with the use of novel agents such as mogamulizumab.[9-11]

Over the past decade, allogeneic hematopoietic cell transplantation (HCT) has been increasingly performed with the aim of improving dismal prognosis of patients who developed ATL.[12-18] Notably, some patients with ATL who relapsed after allogeneic HCT were shown to achieve remission only with the cessation of immunosuppressive agents, raising the question of whether the graft-versus-leukemia effect against ATL can be induced as part of graft-versus-host reaction.[19,20] In 1 study, among 10 patients who experienced relapse of ATL after transplantation and were withdrawn from immunosuppressive therapy, 8 developed graft-versus-host disease (GVHD), and 6 of them subsequently achieved

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