Leukemia Research 79 (2019) 3–5

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Letter to the Editor

Chronic myeloid leukemia: Two mysteries

Few causes of CML are known, the most important of which is exposure to ionizing radiations (reviewed in [1]). A-bomb survivors from Hiroshima and Nagasaki [2] are central to understanding the biology of CML because in many survivors with CML it is almost certain *BCRABL1* was formed when the A-bombs exploded. A re-examination of A-bomb survivor data reveals two mysteries. The 1st is CML was increased in Hiroshima but not Nagasaki survivors > 20 years of age exposed to > 200 mSv radiation. The 2nd is amongst Hiroshima survivors exposed to > 1 Sv who developed CML, most females developed it about 15 years later than males.

Mystery 1: Why no CML in Nagasaki A-bomb survivors > 20 years of age exposed to > 200 mSv versus a substantial increase in seemingly similar Hiroshima survivors?

US Surveillance, Epidemiology and End Results (SEER) data for race classification *other* (not white or black; Fig. 1A) enables estimates of how many cases of CML would be expected in an unexposed US cohort age- and sex-matched to Nagasaki A-bomb survivors exposed to > 200 mSv. The same can be done for similar Hiroshima A-bomb survivors. When we did this for Nagasaki A-bomb survivors there were no CML cases *versus* 1.5 expected. The observed/expected ratio (O/E), or relative risk (RR), was 0 (95% confidence interval 0, 2.45, assuming O is Poisson distributed). This contrasts with data from the Hiroshima A-bomb survivors where in the similarly exposed (> 200 mSv) cohort there were 29 cases of CML observed *versus* 5 expected had they not been exposed (O/E = RR = 5.8 [3.88, 8.33]). This discordance was not observed in persons < 20 years exposed to > 200 mSv: in Nagasaki vs Hiroshima O/E was 2/0.1 (RR = 200 [24.2–700]) *versus* 3/0.03 (RR = 100 [20–292]), P = 0.8 (interestingly, all 5 were males, Table 1). Also, across all ages of persons exposed to < 200 mSv we found O/E = 9/11.3 (RR = 0.80 [0.36–1.5]) in Nagasaki and 24/25.1 (RR = 0.94 [0.60–1.39]) in Hiroshima, with no apparent sex differences (Table 1). Fig. 1B summarizes these data. The bottom line is in persons > 20 years exposed to > 200 mSv, CML was markedly increased in Hiroshima but not Nagasaki A-bomb survivors. Why?

Mystery 2: Why was CML onset later in Hiroshima female versus male A-bomb survivors?

In Hiroshima A-bomb survivors exposed to > 1 Sv, 16 cases of CML were observed *versus* 0.96 cases expected (RR = 16.6 [9.5, 27]) indicating almost all cases were caused by A-bomb ionizing radiations. Although we expect females and males to be diagnosed with CML after similar intervals following A-bomb exposure, median female and male latencies were 25 (range, 9.1–28.7) and 8.5 years (range, 6.1–38.5; P = 0.02; Fig. 1C). Thus, either the latency in males was accelerated or the latency in females was delayed. Fitting $m = (1 + k^3t^2e^{c-kt})E$ to CML cases after thyroid cancer treated with radioactive iodine ^{131}I in the SEER dataset (using all races combined, Fig. 1D) yielded no sex differences in c and k and a latency of 6.1 years (95% confidence interval 4.8, 8.3), consistent with the latency for Hiroshima males considering A-bomb survivor onsets < 5 years were left-censored (the Atomic Bomb Casualty Commission began leukemia surveillance in 1950). CML onsets for Hiroshima females exposed to > 1 Sv were thus delayed approximately 3-fold. Why?

Mysteries 1 and 2 are difficult to explain. Although few data support immune surveillance for CML [3], Mystery 1 could involve Nagasaki-Hiroshima differences in infection rates of human T-cell leukemia-lymphoma virus-1 (HTLV-1) [2] and thus differences in immunity [4]. Mystery 2 could involve increased immune competency in females [5]. An added complexity, however, is immune system involvement dependence on *whole-body* radiation. It will be difficult to prove or disprove proposed mechanisms of whole-body radiation interactions with immunity but discussions may provoke more careful thinking about how much we really understand the biology of CML. They could also kindle interest in mimicking whole-body radiation effects through irradiated cell vaccines: beyond a model for therapy, understanding CML could help it become a model for prevention.

https://doi.org/10.1016/j.leukres.2019.02.003
Received 8 February 2019
Available online 12 February 2019

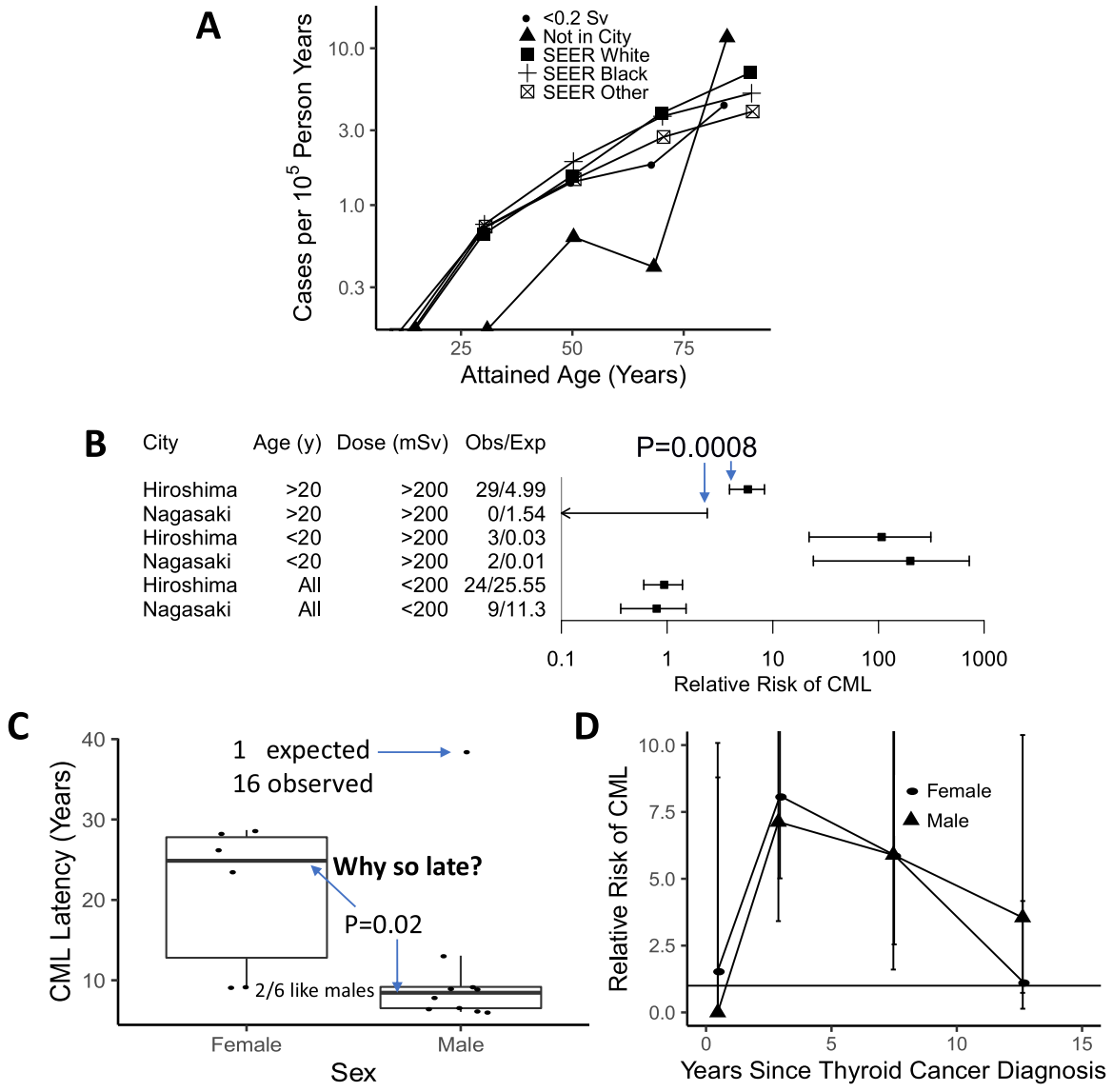

Fig. 1. Japanese A-bomb survivor data and Surveillance and Epidemiological End Results (SEER) data. **A)** SEER-based expected numbers of CML cases if A-bomb survivors were not irradiated. SEER race other (not black or white) age-specific incidence rates are consistent with the A-bomb survivor low dose (< 200 mSv) group. To the extent that this is unlikely to be a coincidence, this substantiates CML induction negligibility in the dose group < 200 mSv and use of SEER race other as a control group. The dose group "not-in-city at time of bombing" is inconsistent with both of these groups and is thus ignored in our analyses. **B)** No CML in Nagasaki in those > 20 y exposed to > 200 mSv. Sex specific details are provided in Table 1. P = 0.0008 was determined by a Poisson rate ratio test (using the R package rateratio.test). **C)** Delays in CML onsets in Hiroshima females exposed to > 1 Sv (P = 0.02; Wilcoxon Rank Sum Test). **D)** No sex differences in SEER (1973–2015) CML risks after thyroid cancers treated with ^{131}I. No sex differences in the fitted parameters of the smooth curve shown imply similar male and female latencies. The smooth curve is m/E where $m = (1 + k^3t^2e^{c-kt})E$ was fitted using Poisson regression to SEER CML cases after thyroid cancer treated with radiation; here E is the number of CML cases expected if the person years at risk after thyroid cancer were randomly selected from the US population, matched for age and sex, and k and c are excess risk time-scale and amplitude parameters, respectively. There were no sex differences in k or c and thus no sex differences in latency.

Table 1
A-bomb survivor CML cases observed and expected if subjects were not exposed.

1950-2001		Nagasaki						Hiroshima					
		Males			Females			Males			Females		
Dose	Age	Obs[a]	Exp[a]	Tsx[a]	Obs	Exp	Tsx	Obs	Exp	Tsx	Obs	Exp	Tsx
> 1 Sv	[0,20]	1	0.002	8.9	0	0.001		2	0.003	8.6	0	0.002	
> 1 Sv	(20,40]	0	0.041		0	0.024		3	0.067	7.3	2	0.039	19
> 1 Sv	(40,60]	0	0.093		0	0.074		3	0.169	7.2	1	0.159	24
> 1 Sv	(60,80]	0	0.1		0	0.09		1	0.23	13	3	0.211	21
> 1 Sv	> 80	0	0.015		0	0.011		1	0.037	39	0	0.038	
0.2-1 Sv	[0,20]	1	0.004	9	0	0.003		1	0.014	9.1	0	0.009	
0.2-1 Sv	(20,40]	0	0.087		0	0.056		2	0.227	16	0	0.157	
0.2-1 Sv	(40,60]	0	0.195		0	0.188		3	0.591	21	4	0.706	10
0.2-1 Sv	(60,80]	0	0.236		0	0.252		1	0.831	11	5	1.106	22
0.2-1 Sv	> 80	0	0.035		0	0.04		0	0.166		0	0.257	
< 0.2 Sv	[0,20]	0	0.061		0	0.035		0	0.094		0	0.055	
< 0.2 Sv	(20,40]	1	0.889	11	0	0.521		2	1.634	20	1	0.958	14
< 0.2 Sv	(40,60]	3	1.833	36	3	1.972	42	4	3.962	29	2	4.237	27
< 0.2 Sv	(60,80]	1	2.206	17	1	2.823	34	5	5.385	28	5	6.553	32
< 0.2 Sv	> 80	0	0.369		0	0.592		1	1.075	31	4	1.597	37
> 1 Sv	all	1	0.251	8.9	0	0.2		10	0.506	15	6	0.449	21
0.2-1 Sv	all	1	0.557	9	0	0.539		7	1.829	14	9	2.235	16
< 0.2 Sv	all	5	5.358	21	4	5.943	38	12	12.15	27	12	13.4	27

[a] Obs = observed number of CML cases; Exp = expected number of CML cases based on SEER data using race other (not black or white); Tsx = time-since-exposure of CML diagnoses in years.

Conflicts of interest

RPG is a part-time employee of Celgene Corp. There are no other conflicts.

Contributions

All authors contributed writing to this typescript. R scripts freely available in https://github.com/radivot/SEERaBomb/tree/master/SEERaBomb/inst/docs/papers/CMLmysteries were written by TR. This report is the sole responsibility of the authors; it does not represent the views of the National Cancer Institute (NCI), the Radiation Effects Research Foundation (RERF), or others.

References

[1] T. Radivoyevitch, L. Hlatky, J. Landaw, R.K. Sachs, Quantitative modeling of chronic myeloid leukemia: insights from radiobiology, Blood 119 (2012) 4363–4371.
[2] W.L. Hsu, D.L. Preston, M. Soda, H. Sugiyama, S. Funamoto, K. Kodama, et al., The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950-2001, Radiat. Res. 179 (2013) 361–382.
[3] R.P. Gale, G. Opelz, Is there immune surveillance against chronic myeloid leukaemia? Possibly, but not much, Leuk. Res. 57 (2017) 109–111.
[4] J.A. Quaresma, G.T. Yoshikawa, R.V. Koyama, G.A. Dias, S. Fujihara, H.T. Fuzii, HTLV-1, immune response and autoimmunity, Viruses 8 (2015).
[5] T.N. Jorgensen, Sex disparities in the immune response, Cell. Immunol. 294 (2015) 61–62.

Tomas Radivoyevitch*
Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, USA
E-mail address: radivot@ccf.org.

Trine N. Jorgensen
Inflammation and Immunity, Lerner Research Institute, Cleveland Clinic, Cleveland, USA

Daniel J. Lindner, Jaroslaw P. Maciejewski
Translational Hematology and Oncology Research, Lerner Research Institute, Cleveland Clinic, Cleveland, USA

Yasushi Miyazaki
Department of Hematology, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, Japan

Robert Peter Gale
Haematology Research Centre, Imperial College London, London, UK

* Corresponding author at: Department of Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic, JJN3-01, 9500 Euclid, Cleveland, OH 44195, USA.