

## Imatinib withdrawal syndrome and longer duration of imatinib have a close association with a lower molecular relapse after treatment discontinuation: the KID study

Sung-Eun Lee,<sup>1</sup> Soo Young Choi,<sup>1</sup> Hye-Young Song,<sup>1</sup> Soo-Hyun Kim,<sup>1</sup> Mi-Yeon Choi,<sup>1</sup> Joon Seong Park,<sup>2</sup> Hyeoung-Joon Kim,<sup>3</sup> Sung-Hyun Kim,<sup>4</sup> Dae Young Zang,<sup>5</sup> Sukjoong Oh,<sup>6</sup> Hawk Kim,<sup>7</sup> Young Rok Do,<sup>8</sup> Jae-Yong Kwak,<sup>9</sup> Jeong-A Kim,<sup>10</sup> Dae-Young Kim,<sup>11</sup> Yeung-Chul Mun,<sup>12</sup> Won Sik Lee,<sup>13</sup> Myung Hee Chang,<sup>14</sup> Jinny Park,<sup>15</sup> Ji Hyun Kwon,<sup>16</sup> and Dong-Wook Kim<sup>1,17</sup>

<sup>1</sup>Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul; <sup>2</sup>Department of Hematology-Oncology, Ajou University School of Medicine, Suwon; <sup>3</sup>Department of Hematology-Oncology, Chonnam National University Hwasun, Hospital; <sup>4</sup>Department of Internal Medicine, Dong-A University College of Medicine, Busan; <sup>5</sup>Department of Internal Medicine, Hallym University College of Medicine, Anyang; <sup>6</sup>Division of Hematology-Oncology, Department of Internal Medicine, Kangbuk Samsung Hospital, School of Medicine, Sungkyunkwan University, Seoul; <sup>7</sup>Division of Hematology and Cellular Therapy, Ulsan University Hospital, University of Ulsan College of Medicine; <sup>8</sup>Division of Hematology-Oncology, School of Medicine, Keimyung University, Daegu; <sup>9</sup>Division of Hematology-Oncology, Chonbuk National University Medical School, Jeonju; <sup>10</sup>Department of Hematology, St. Vincent's Hospital, The Catholic University of Korea, Suwon; <sup>11</sup>Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Seoul; <sup>12</sup>Department of Hematology, School of Medicine, Ewha Womans University, Seoul; <sup>13</sup>Department of Internal Medicine, Inje University College of Medicine, Inje University Busan Paik Hospital; <sup>14</sup>Department of Hematology-Oncology, National Health Insurance Service Ilsan Hospital, Ilsan; <sup>15</sup>Department of Hematology, Gachon University Gil Hospital, Incheon; <sup>16</sup>Department of Hematology-Oncology, Chungbuk National University Hospital, Cheongju; and <sup>17</sup>Catholic Leukemia Research Institute, The Catholic University of Korea, Seoul, Korea

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Correspondence: dwkim@catholic.ac.kr

## **Supplementary Methods**

### **Digital PCR**

dPCR was performed using the BioMark Real-Time PCR System (Fluidigm, USA) and 12.765 Digital Array (Fluidigm). Each of 12 samples was automatically partitioned into 765 chambers. cDNA was pre-amplified using primers specific for *BCR-ABL1* and a probe to increase the number of target copies, and the pre-amplification product was analyzed by dPCR. After completion of 40 cycles of thermal cycling, BioMark Digital PCR Analysis Software was used to calculate the number of positives in each panel and data were generated as heat maps with corresponding amplification curves for each of the 765 chambers.

**Supplementary Table 1. Characteristics of patients with aggravation or new development of musculoskeletal pain after IM discontinuation**

Patient	Sex/ Age (yr)	IM therapy duration (months)	Aggravation or new development after IM cessation	Localization of symptoms	Onset time from IM cessation <sup>†</sup> (months)	Duration of symptoms from IM cessation (months)	CPK eleva- tion	Effect of therapy				F/U duration from IM cessation (months)	Loss of MMR (Time to loss of MMR, months)	Loss of UMRD (Time to loss of MMR, months)
								Paracetamol	NSAID	Steroids	Others			
1	M/44	85.9	New development	Hands, feet	1	1	No	-	-	-	-	42.5	-	-
2	F/58	108.0	New development	Hands, calves, feet	3	36 (on-going)	No	+(partial response)	-	-	Oxycodone (partial response)	39.3	-	-
3	F/72	129	New development	Whole body	1	12	No	-	-	+(partial response)	-	29.7	Yes (20.8)	Yes (7.2)
4	F/58	129	Aggravation	Shoulder, back	-	8	No	-	-	-	-	29.7	-	-
5	F/51	56.9	New development	Calves, hands, shoulder	3	25	No	+(partial response)	-	-	-	29.5	-	-
6*	M/52	111	New development	Upper arms	2	16	No	+(partial response)	+(complete response)	-	-	29.0	-	-
7	F/61	43.4	New development	Shoulder	1	6	Yes	-	-	-	-	25.7	Yes (3.6)	Yes (2.7)
8	F/48	50.2	Aggravation	Whole body	-	8	No	+(partial response)	-	+(partial response)	-	24.8	-	-
9	M/48	113.8	Aggravation	Hands, feet, lower back	-	10	No	-	-	-	-	23.7	-	-
10	F/76	53	Aggravation	Calves, thighs	-	4	No	-	-	-	-	20.2	-	-
11	M/51	69.3	Aggravation	Hands, feet, lower back	-	6	Yes	+(partial response)	-	-	-	19.8	-	Yes (3.0)
12	F/47	50.5	New development	Hands, calves, feet	1	1	No	-	-	-	-	19.1	-	-
13	F/67	107.1	New development	Hands, neck, knees	1	6	No	-	+(partial response)	-	-	17.6	-	-
14	F/51	89.0	New development	Hands, knees	2	3	No	-	-	-	-	28.8	-	-
15	M/42	87.0	New development	Hands, feet	2	3	No	-	-	-	-	55.6	-	-
16	F/67	141.2	New development	Hands, shoulder	1	6	No	+(partial response)	+(partial response)	-	-	12.9	-	-

Abbreviations: CPK, creatine phosphokinase; NSAID, nonsteroidal anti-inflammatory drug; F/U, follow-up

\* Patient #6 developed both musculoskeletal pain and pruritus after IM cessation.

† The median time of onset was 1 month (range, 1-3 months).

**Supplementary Table 2. Characteristics of patients with aggravation or new development of pruritus after IM cessation**

Patients	Sex/age (yrs)	IM therapy duration (months)	Aggravation or new development after IM cessation	First symptom onset from IM cessation <sup>†</sup> (months)	Duration of symptoms from IM cessation (months)	Effect of therapy			F/U duration from IM cessation (months)	Loss of MMR (Time to loss of MMR, months)	Loss of UMRD (Time to loss of UMRD months)
						Steroids	Anti-histamine	NSAID			
1	F/50	83.5	New development	2	3	-	-	-	58.1	-	-
2	F/59	103.6	New development	1	54 (ongoing)	+(partial response)	+(partial response)	-	55.1	-	-
3	F/41	76.8	New development	1	3	-	-	-	34.7	Yes (7.6)	Yes (2.8)
4	M/49	99.7	New development	1	2	-	-	-	31.7	-	-
5*	M/52	111.0	New development	2	3	-	-	-	29.0	-	-
6	M/67	66.1	New development	2	6	-	+(partial response)	-	28.1	-	-
7	M/73	141.3	New development	1	2	-	-	-	24.5	-	-
8	F/72	52.1	New development	1	6	-	+(partial response)	-	20.4	Yes (12.2)	Yes (3.7)
9	F/32	82.2	New development	1	2	-	-	-	20.1	-	-
10	F/67	115.2	New development	8	10 (ongoing)	-	-	-	17.5	-	-
11	F/47	68.5	New development	3	2	-	-	-	15.4	-	-
12	F/63	140.7	New development	2	8	+(partial response)	-	-	13.4	Yes (6.6)	Yes (3.8)

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; F/U, follow-up; UMRD, undetectable molecular residual disease; MMR, major molecular response.

\* Patient #5 developed both musculoskeletal pain and pruritus after IM cessation.

† The median time of onset was 1.5 months (range, 1-8 months).

**Supplementary Figure 1. Comparison of the creatine phosphokinase (CPK) level between patients with and without IMWS.** Among 58 patients with available serial data of CPK, mean value of CPK did not show difference between two groups ( $106.11 \pm 14.07$  U/L vs.  $124.16 \pm 19.95$  U/L,  $P = 0.543$ ).

