Original Article

Retrospective Karyotype Analysis of 12,261 Cases with Hematological Malignancy

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Objective: To report characteristics and number of chromosome abnormalities detected in samples collected from patients suspected of having haematological malignancy by clinicians.

Materials and Methods: We retrospectively reviewed karyotype data of 12,261 newly diagnosed haematological malignancy and follow-up cases who received conventional cytogenetic analyses at Cancer Cytogenetics Unit, Chulabhorn Hospital between 2009 and 2015.

Results: Among the total suspected and follow-up haematological malignancy cases analysed, 35.22% (4,318 cases) had chromosomal aberrations while the other 64.78% (7,943 cases) showed normal chromosome arrangements. Among the patients with chromosomal aberrations, there were 734 cases with numerical aberrations, another 2,621 cases with structural aberrations, and a further 963 cases reported with both numerical and structural aberrations. Moreover, we discovered in Thai chronic myelogenous leukaemia [CML] patients with complex translocations that a third and fourth chromosome were sometimes involved with the Philadelphia chromosome (9; 22) (q34; q11), creating three-way and four-way translocations.

Conclusion: The present study compiles the karyotypic analysis of 12,261 haematological cases which represents the largest dataset from Thailand. Chromosomal aberrations were found in one-third of total cases. Our information should be of value to include in a national cancer registry.

Keywords: chromosome, haematological malignancy, karyotype, conventional cytogenetics, chromosomal aberrations

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In Thailand, patients diagnosed with leukaemia in both adults and children between 1995 and 2009 accounted for 3.6% of all cancer patients(1). An incidence report in 1996 showed that the incidence of non-Hodgkin lymphoma [NHL], Hodgkin's disease, and leukaemia were 4.3, 0.4, and 3.9 per 100,000 population in male patients and 3.1, 0.3, and 3.4 per 100,000 population in female patients(2). For the northern region of Thailand, a study in 2005 showed that leukaemia in the male population ranked 9th, accounting for around 2.9% of the total number of cancer cases. In the female population, it was reported that NHL ranked 6th, accounting for around 4.5% of the total number of cancer cases. In the north-eastern region of Thailand, NHL and leukaemia were reported to account for 5.1% and 4.7% of cancer cases in the male population, respectively. In the female population, it was reported that NHL accounted for 3.85% of the total number of cancer cases found. The national cancer database in Thailand registered that in 2012 the number of new cases of haematological malignancy (Hodgkin lymphoma, NHL, multiple myeloma, and leukaemia)

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were reported as 5.3% and 3.2% of cancer cases in the male and female population, respectively.

In 2016, the World Health Organisation[3] has recently proposed a new classification of myeloid and lymphoid neoplasms[3]. A variety of diagnostic tools are needed to correctly identify and categorize haematological malignancy. Conventional cytogenetics has contributed towards diagnosis, staging, prognosis, treatment, treatment response evaluation and understanding of disease biology. Chromosome banding analysis is among other molecular cytogenetics techniques that are used to define the particular genetic subtype of leukemias[4]. The WHO describes cytogenetics as the study of chromosomes and of the disease states caused by numerical and structural chromosome abnormalities[5]. Conventional cytogenetic diagnostic tool is a clonal and single-cell-based genomic screening method that has been considered the gold standard to detect chromosomal aberrations in haematological diseases[6]. Using the most up to date series of WHO classification 2016, conventional cytogenetic diagnostic tool can benefit the patients suffering from haematological malignancies. For example, lists of cytogenetic abnormalities that now define AML with myelodysplasia-related changes are illustrated in the WHO Classification of Tumours, highlighting the continuing relevance of chromosome diagnosis to WHO Classification[7]. Although cytogenetic and genetic abnormalities may be identified by various diagnostic tools such as fluorescence in situ hybridization [FISH], reverse transcriptase polymerase chain reaction [RT-PCR], array-based comparative genomic hybridization [aCGH] and single nucleotide polymorphism [SNP] arrays to detect copy number aberration, conventional cytogenetic remains an essential tool in the practice of chromosomal diagnostic work-up of haematological malignancy[8].

The present study aimed to report the descriptive data of patients diagnosed with haematological malignancies and to give an overview of conventional cytogenetic technique (Q-banding) results from all haematological malignancy cases from 2009 to 2015, and to provide information about the trends in the different types of haematological malignancies.

Materials and Methods

Patient samples

This study was reviewed and approved by the Ethical Committee for Human Research of Chulabhorn Research Institute (EC No. 11/2559). Heparinised bone marrow aspirates or peripheral blood samples from patients in this study were sent to the Cytogenetic Department at Chulabhorn Hospital by clinicians following routine diagnosis at Chulabhorn Hospital or at other hospitals in Thailand. During the transportation of the samples to Chulabhorn Hospital, their temperature was kept at 4°C. Once the samples reached the laboratory, they were cultured within 24 hours from the initial extraction from the patient. A total of 12,261 samples with successful karyotypes were recruited to this study from January 2009 to November 2015. Each sample was collected for a routine cytogenetic study in our laboratory.

Conventional cytogenetic study

Cultures of cells from bone marrow or peripheral blood from patients were incubated in RPMI 1,640 medium (Biological Industries) supplemented with 20% foetal bovine serum (Biological Industries and Biochrome AG) for 16 to 24 hours at 37°C in an atmosphere of 5% CO_2. Cell harvest was completed by standard laboratory procedures. Chromosomes were carefully spread from harvested cells on a glass slide. All samples were Q-banded by staining with Quinacrine mustard (Sigma) according to standard laboratory procedures. A minimum of 40 scanning images were collected using Metafer software (MetaSystems). Chromosome scanning was done with an automated Zeiss Axio Imager. Z2 equipped with a CCD-camera (CoolCube1). Image capture was done with a Zeiss AXIO Scope.A1 equipped with a CCD-camera (CoolCube1) using Relosis software (MetaSystems). Culturing and analyses were all completed within a single laboratory to improve the precision of the experiments. A minimum of 40 images were scanned and captured. The images were converted from Q-banding into G-banding for analysis using the Ikaros program. Analyses of at least 20 cells were completed by three independent observers. The chromosomal abnormalities were described according to ISCN (ISCN 2009 and 2013).

Statistical analysis

Data collection was performed using Microsoft Office Excel. The karyotypes of the patients were summarised for all patients using descriptive statistics.

Results

The present study included 12,261 cases of patients suspected of or followed-up for having

Table 1. Summary of haematological malignancies analysed by conventional Q-banding cytogenetics techniques from 2009 to 2015

Clinical diagnosis	Total number of cases	Normal karyotype	Abnormal karyotype
Total cases	12,261	7,943	4,318
Leukaemia	410	245	165
Acute leukaemia (not specified)	459	262	197
Acute myeloid leukaemia and acute promyelocytic leukemia [APL]	2,146	1,113	1,033
Acute lymphoblastic leukaemia (1)	1,125	680	445
Myeloproliferative neoplasm (unclassified)	358	301	57
Chronic myelogenous leukaemia [CML]	3,118	1,526	1,592
CML post imatinib	84	49	35
Polycythaemia vera [PV]	183	172	11
Essential thrombocytosis	40	34	6
Agnogenic myeloid metaplasia [AMM]	5	2	3
MDS	1,515	1,273	242
Others			
Anaemia	394	343	51
Bicytopenia	68	54	14
Eosinophilia	33	31	2
Pancytopenia	693	541	152
Thrombocytopenia	257	221	36
Thrombocytosis	171	156	15
Lymphoma (unclassified)	147	128	19
Non-hodgkin lymphoma [NHL]	82	71	11
Multiple myeloma	129	116	13
Chronic lymphocytic leukaemia [CLL]	111	85	26
Not specified	733	540	193

haematological malignancy. The haematological malignancy cases are presented in Table 1, showing that of the total diagnosed (n = 12,261), approximately one-third of the cases had abnormal karyotypes (n = 4,318), whereas the remaining suspected and follow-up patients showed a normal karyotype (n = 7,943) when diagnosed using a conventional cytogenetic method.

The total number of cases diagnosed with leukaemia and acute leukaemia accounted for 3.34% (n = 410) and 3.74% (n = 459) of the total, respectively. The reason behind the diagnoses given to these groups was that prior to the patient's sample reaching Chulabhorn Hospital, on the request form after initial examination by clinicians, they could not be placed in any specific subtype of myeloid or lymphoid neoplasm. Therefore, a generalised name was created for these 869 cases. The analyses of chromosomal karyotype were completed using the diagnoses of leukaemia and acute leukaemia. Chromosomal aberrations were detected in 40.24% (n = 165) from a total of 410 cases of leukaemia and 42.92% (n = 197) from a total of 459 cases of acute leukaemia.

Table 1 shows the various types of diagnostic diseases and disorders. They are arranged to show the number of cases that had normal and abnormal karyotypes. The most common diagnosis was chronic myelogenous leukaemia [CML] making up 25.43% (n = 3,118) of the total cases. An abnormal karyotype was detected in approximately 51.06% (n = 1,592) of CML cases. Acute myeloid leukaemias [AML], which includes APL, was the second-most common diagnosis, at 17.5% (n = 2,146) of the total cases. An abnormal karyotype was found in 48.14% (n = 1,033) of cases. The third-most common diagnosis was myelodysplastic syndromes [MDS] with 12.36% (n = 1,515) of the total cases. MDS cases often had a normal karyotype, 84.03% (n = 1,273), and an abnormal karyotype was found in only 15.97% (n = 242). Following MDS, the next most common diagnosis was acute lymphoblastic leukaemia (1) with 9.17% (n = 1,125) of total cases. In ALL, an abnormal karyotype was detected in 39.56% (n = 445).

Myeloproliferative neoplasms (unclassified) were reported as the diagnosis for 2.92% (n = 358) of the total number. In these 358 cases, only 15.92% (n = 57) had a chromosomal abnormality. In CML post imatinib treatment samples, only 84 cases in total were collected with 41.67% (n = 35) showing chromosomal aberrations. Chromosomal analyses of polycythaemia vera [PV] included 183 cases with 6.01% (n = 11) exhibiting chromosomal aberrations. Essential thrombocytosis had only 40 cases and 15% (n = 6) had chromosomal abnormalities. Eosinophilia had the second-lowest total number of cases with 33 and only 6.06% (n = 2) had chromosomal abnormalities. The least-common diagnosis was agnogenic myeloid metaplasia [AMM] with only 5 cases and 60% (n = 3) of these had a chromosomal abnormality.

In the other subgroup, anaemia was reported for 394 cases in total with only 12.94% (n = 51) showing chromosomal aberrations. Thrombocytopenia and thrombocytosis had 257 and 171 cases in total, respectively. Both diseases had a majority of normal karyotypes, with only 14.01% (n = 36) and 8.77% (n = 15) of thrombocytopenia and thrombocytosis cases, respectively, having chromosomal abnormalities. For bicytopenia, there were 68 cases in total with only 20.59% (n = 14) having chromosomal aberrations. Chromosomal analysis of pancytopenia had 693 cases in total with only 21.93% (n = 152) having chromosomal aberrations.

In the lymphoma (unclassified) group, there were 147 cases in total, and 12.93% (n = 19) had chromosomal aberrations. This lymphoma (unclassified) group was created for patients who could not be specifically identified as to the type of lymphoid neoplasm. Moreover, non-Hodgkin lymphoma [NHL] was reported with 82 cases in total and 13.41% (n = 11) showed chromosomal aberrations. The group of patients with multiple myeloma included only 129 cases and only 10.08% (n = 13) had chromosomal aberrations. Chronic lymphocytic leukaemia [CLL] was diagnosed in 111 cases and 23.42% (n = 26) had a chromosomal aberration. The last group, Not specified, accounted for 733 cases, and using conventional cytogenetic techniques, 26.33% (n = 193) had an abnormal karyotype across the 7-year period.

Using the conventional cytogenetic method of Q-banding, it was possible to categorise chromosomal aberrations in the cases into four groups (Table 2). The four groups were numerical aberration, structural aberration, complex (numerical and structural aberration), and normal chromosome karyotype.

Table 2. Types of chromosome aberrations detected in patients suspected with haematological malignancies from 2009 to 2015

Chromosome karyotype	Total cases (%)
Numerical aberration	5.99
Structural aberration	21.38
Structural and numerical complex	7.85
Normal	64.78

Numerical aberration causes a change in chromosome number and makes up a significant proportion of chromosomal changes found in humans. Common examples of numerical aberrations are trisomy, monosomy, and polyploidy. The other simple type, structural aberration, represents a loss of genetic material or a rearrangement in the location of the genetic material. A few examples of structural aberrations are deletions, duplications, inversions, translocations, and ring formations. The remaining complex group includes samples that contain both numerical and structural aberrations.

The total number of samples with normal chromosome karyotypes was 64.78% (n = 7,943). Numerical aberrations accounted for 5.99% (n = 734) of the sample, structural aberrations for 21.38% (n = 2,621), and complex cases with both numerical and structural aberrations accounted for 7.85% (n = 963) of the total number of cases.

Philadelphia chromosome translocations t (9; 22) detected in CML, AML, and CML post imatinib are shown in Table 3. The number of t (9; 22) detected in abnormal karyotypes of suspected CML patients was 67.27%, with 77.14% detected in abnormal karyotypes of CML post imatinib patients' samples. In addition, three-way and four-way translocations involving the Philadelphia chromosome were detected in 104 and 9 cases, respectively.

In Figure 1, several three-way translocation examples are shown. These three-way Philadelphia translocations t (9; 22; 13) (q34; q11.2; q14), t (9; 22; 7) (q34; q11.2; q11.2), t (9; 22; 6) (q34; q11.2; p21.3), and t (9; 22; 11) (q34; q11.2; p13) were detected from patients suspected of having CML, in whom the majority of translocations t (9; 22) occurred. Another example of a translocation is shown in Figure 2, a four-way translocation t (9; 22; 8; 12) (q34; q11.2; q22; q24.1). Other cytogenetic abnormalities reported were additional material of unknown origin, deletion of chromosomes or chromosome bands, and additional

Table 3. Philadelphia chromosome in CML, AML, and CML (post-imatinib treatment) from patient samples collected from 2009 to 2015

Philadelphia Chromosome	CML, total (n = 1,362)	AML, total (n = 91)	CML post-imatinib, total (n = 30)
t (9;22)	1,071 (78.63%)	45 (49.45%)	27 (90%)
t (9;22) with numerical and structural aberration	178 (13.07%)	46 (50.55%)	3 (10%)
Three-way translocation	104 (7.64%)	N/A	N/A
Four-way translocation	9 (0.66%)	N/A	N/A

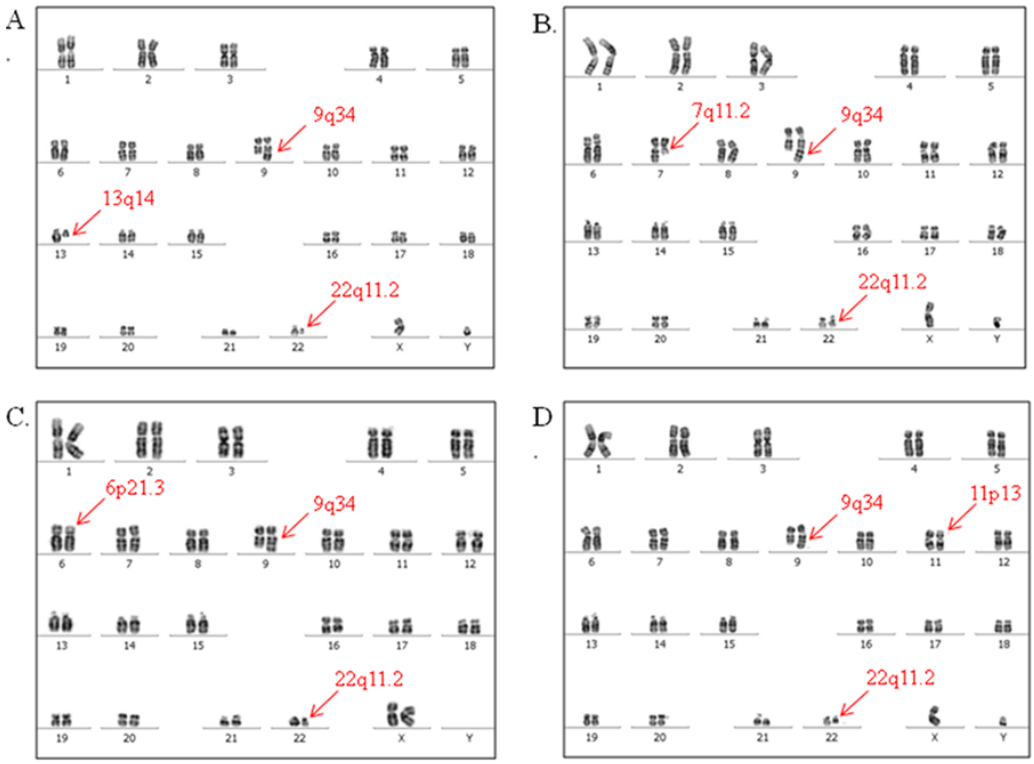

Figure 1. Three-way Philadelphia translocation.

normal or abnormal chromosomes (data not shown).

Discussion

In this report, we established that the numbers of suspected haematological malignancies cases were 12,261 from January 2009 to November 2015 with approximately 35% of the total number of cases showing chromosomal abnormalities after conventional cytogenetic analysis. Our data demonstrated that the majority of patients suspected of having haematological malignancies had normal karyotypes. However, it is possible that this is because we were limited to only conventional cytogenetics in the present study. More sensitive diagnostic techniques such as fluorescence in situ hybridization [FISH], polymerase chain reaction, and comparative genomic hybridization may have decreased the number of cases with a normal karyotype and provided more specific data in cases with abnormal karyotypes[9,10].

The haematological malignancy that had the largest percentage of chromosomal aberrations detected was CML. It has been reported that the Philadelphia translocation t (9; 22) is present in 90% to 95% of patients with CML[11]. However, our report

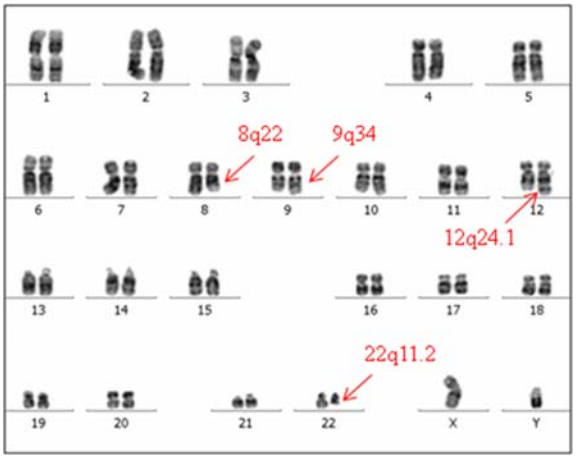

Figure 2. Four-way Philadelphia chromosome detected with Q-banding in a patient suspected with CML.

shows a positive Philadelphia translocation t (9; 22) in only 85.55% of CML cases with an abnormal karyotype. This should be interpreted with caution because we cannot demonstrate with our available data that all of our patients suspected of having CML were actually finally diagnosed with it.

Another translocation identified in this report is t (8; 21). Translocation t (8; 21) involves fusion of the acute myeloid leukaemia 1 [AML1] gene on chromosome 21 to the eight twenty-one [ETO] gene on chromosome 8 to create an AML1-ETO fusion gene[12]. Our report shows that positive t (8; 21) was detected in 6.67% of the patient bone marrow and peripheral blood samples sent for AML and ANLL cytogenetic analysis. This finding is consistent with a previous report showing a positive t (8; 21) (q22; q22) translocation was found in approximately 5% to 10% of all AML cases[13]. AML is more common in children and younger patients who have a higher probability of chromosomal abnormalities, and the number of positive t (8; 21) cases decreases with increasing age[14].

The other common translocation pattern is t (15; 17). This translocation fuses the retinoic acid receptor alpha [RARA] gene on chromosome 17 to the promyelocytic leukaemia [PML] gene on chromosome 15, resulting in the formation of a PML-RARA gene fusion product[15,16]. This PML-RARA fusion gene transcript has a crucial role in the pathogenesis of APL, where approximately 70% to 80% of patients with newly diagnosed APL are reported to have PML-RARA experience long-term remission[17]. We also found that the t (15; 17) (q24; q21) translocation is detected in 60.4% of APL cases that show chromosomal abnormalities and 10.39% of all AML, ANLL, and APL cases. Furthermore, additional abnormalities were commonly detected in association with the t (15; 17) translocation, including additional normal or abnormal chromosomes, deletions, derivatives, insertions, and inversions. In some cases involving t (15; 17) translocations, cytogenetic analysis revealed a variant three-way translocation, for example 46, XX, t (1; 15; 17) (p36.1; q24; q21).

Using conventional cytogenetic analysis, this report showed examples of several three-way translocations in CML. A variant three-way involving the Philadelphia translocation was present in 6.53% of the CML cases that showed chromosomal abnormalities. This finding is consistent with the report by La Starza et al[18], who found variant complex translocations involving a third chromosome in 5% to 8% of CML patients. However, in rare cases, a fourth chromosome is also involved. A four-way translocation is not frequently detected in CML patients and it is observed more often in male than in female patients[19]. In this report, a four-way translocation was detected in only 0.57% of CML cases that showed chromosomal abnormalities, with nine cases from male patients. However, it is worth mentioning that in the future, using FISH probes or whole genomic sequencing is likely to show more accurately the break points and confirm the three-way and four-way translocations involving the Philadelphia chromosome.

Examples of cases with a three-way transloca tion in 4 patients suspected of CML. Q-banding analysis of cultured bone marrow cells from a 67-year-old man shows translocation (9; 22; 13) (A). A 22-year-old man shows translocation (9; 22; 7) (B). A 43-year-old woman shows translocation (9; 22; 6) (C). A 52-year-old man shows translocation (9; 22; 11) (D). Arrows indicate the structurally abnormal chromosomes. Conventional cytogenetic analysis of cultured bone marrow cells from a 48-year-old man shows a translocation four-way with a complete karyotype 46, XY, t (9; 22; 8; 12) (q34; q11.2; q22; q24.1). Arrows indicate the structurally abnormal chromosomes.

This study reports the use of the conventional cytogenetic technique as a tool to detect chromosomal abnormalities. Our database could not access the follow-up information of patients detected to have chromosomal abnormalities because we reported only hospital-based cases and the clinical data of these patients were unavailable to our cytogenetic laboratory.

This was the major limitation of this report.

Conclusion

Our study provides a comprehensive analysis of 12,261 suspected haematological cases spanning 7 years. Chromosomal aberrations were found in 4,318 cases (one-third of total cases); the majority of them carried structural aberrations (2,621 cases). Moreover, this study reports many cases of Thai patients with rare three-way and four-way Philadelphia chromosome translocations. Further research avenues can be developed using the information from this study, with the primary aim of improving the diagnosis and treatment outcome of patients.

What is already known on this topic?

Chromosomal aberrations are frequently found in haematological malignancy cases. Conventional cytogenetics plays an important role in the diagnosis and classification of patients with myeloid and lymphoid neoplasms.

What this study adds?

The present study describes the karyotypic analysis of 12,261 haematological cases which represents the largest dataset from Thailand and should be useful to include in a national cancer registry. In addition, to our knowledge, this is the first large series of Thai patients with rare cases of three-way and four-way Philadelphia chromosome translocations.

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Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet 2015;385:977-1010.
2. Sriplung H, Sontipong S, Martin N, Wiangnon S, Vootiprux V, Cheirsilpa A, et al. Cancer incidence in Thailand, 1995-1997. Asian Pac J Cancer Prev 2005;6:276-81.
3. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. WHO Classification of tumours of haematopoietic and lymphoid tissues. Revised 4th ed. Geneva: World Health Organization; 2017.
4. Arsham MS, Barch MJ, Lawce HJ, editors. The AGT cytogenetics laboratory manual. 4th ed. Hoboken, NJ: John Wiley & Sons; 2017.
5. Jaffe ES, Swerdlow SH, Campo E, Pileri SA, Thiele J, Harris NL, et al., editors. International Agency for Research on Cancer (IARC WHO Classification of Tumours). WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC Press; 2008.
6. Heim S, Mitelman F, editors. Cancer cytogenetics. 3rd ed. Hoboken, NJ: Wiley-Blackwell; 2009.
7. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-405.
8. Grange B, Callet-Bauchu E, Salles G, Sujobert P. Advances in the role of cytogenetic analysis in the molecular diagnosis of B-cell lymphomas. Expert Rev Mol Diagn 2017;17:623-32.
9. Kerndrup GB, Kjeldsen E. Acute leukemia cytogenetics: an evaluation of combining G-band karyotyping with multi-color spectral karyotyping. Cancer Genet Cytogenet 2001;124:7-11.
10. Kjeldsen E. Oligo-based aCGH analysis reveals cryptic unbalanced der(6)t(X;6) in pediatric t(12;21)-positive acute lymphoblastic leukemia. ExpMolPathol 2016;101:38-43.
11. Al Achkar W, Wafa A, Ikhtiar A, Liehr T. Three-way Philadelphia translocation t (9; 10; 22) (q34; p11.2; q11.2) as a secondary abnormality in an imatinibmesylate-resistant chronic myeloid leukemia patient. Oncol Lett 2013;5:1656-8.
12. Peterson LF, Zhang DE. The 8;21 translocation in leukemogenesis. Oncogene 2004;23:4255-62.
13. Reikvam H, Hatfield KJ, Kittang AO, Hovland R, Bruserud O. Acute myeloid leukemia with the t (8; 21) translocation: clinical consequences and biological implications. J Biomed Biotechnol 2011;2011:104631.
14. Bacher U, Kern W, Schnittger S, Hiddemann W, Haferlach T, Schoch C. Population-based age-specific incidences of cytogenetic subgroups of acute myeloid leukemia. Haematologica

2005;90: 1502-10.
15. Grignani F, Ferrucci PF, Testa U, Talamo G, Fagioli M, Alcalay M, et al. The acute promyelocytic leukemia-specific PML-RAR alpha fusion protein inhibits differentiation and promotes survival of myeloid precursor cells. Cell 1993;74:423-31.
16. Wafa A, Moassass F, Liehr T, Al Ablog A, Al Achkar W. Acute promyelocytic leukemia with the translocation t (15; 17) (q22; q21) associated with t (1; 2) (q42~43; q11.2~12): a case report. J Med Case Rep 2016;10:203.
17. Manola KN, Karakosta M, Sambani C, Terzoudi G, Pagoni M, Gatsa E, et al. Isochromosome der (17) (q10) t (15; 17) in acute promyelocytic leukemia resulting in an additional copy of the RARA-PML fusion gene: report of 4 cases and review of the literature. Acta Haematol 2010;123:162-70.
18. La Starza R, Testoni N, Lafage-Pochitaloff M, Ruggeri D, Ottaviani E, Perla G, et al. Complex variant Philadelphia translocations involving the short arm of chromosome 6 in chronic myeloid leukemia. Haematologica 2002;87:143-7.
19. Asif M, Jamal MS, Khan AR, Naseer MI, Hussain A, Choudhry H, et al. A Novel four-way complex variant translocation involving chromosome 46, XY, t (4; 9; 19; 22) (q25: q34; p13.3; q11.2) in a chronic myeloid leukemia patient. Front Oncol 2016; 6:124.