원저
Lab Med Online
Vol. 8, No. 2: 41-51, April 2018
https://doi.org/10.3343/lmo.2018.8.2.41

진단혈액학 LMO

혈액종양 진단 시에 관찰되는 자연살해세포활성의 다양성

Variable Natural Killer Cell Activity in Hematological Malignancies at Diagnosis

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Background: Natural killer (NK) cells play a key role in innate immune responses and are an important component of anti-cancer defenses. This study aimed to investigate the clinicopathological characteristics of NK cell activity (NKA) among various hematological malignancies at diagnosis and to evaluate their clinical value as a monitoring marker.
Methods: A total of 111 patients that were newly diagnosed with hematological malignancies were recruited, comprising 18 acute myeloid leukemia (AML), 31 multiple myeloma (MM), and 62 lymphoma. Twenty-three normal control subjects from our health examination center were recruited. NKA was measured using a commercially available enzyme-linked immunosorbent assay kit, which measures interferon-gamma secreted by ex vivo-stimulated NK cells in whole blood.
Results: The 111 patients had a median NKA of 202.80 pg/mL (range 40–2,000). NKA was significantly decreased in patients with AML (median 47.05 pg/mL, 40–2,000, $P<0.0001$), MM (275.00, 40–2,000, $P<0.0001$), and lymphoma (289.49, 40–2,000, $P<0.0001$) compared with that in normal controls (1,891, 412–2,000). There was a difference in NKA between AML and lymphoma ($P=0.0499$). Serial changes in NKA correlated with disease progression. NKA did not correlate with the NK cell count in any group of hematological malignancies.
Conclusions: The measurement of NKA could be useful to evaluate the immunological status in hematological malignancies at diagnosis and during follow-up.

Key Words: Natural killer cells, Interferon-gamma, Clinical application, Hematological malignancy

INTRODUCTION

Natural killer (NK) cells play an important role in innate immune surveillance against malignancy. NK cells exert their cytotoxic activity via perforin and granzyme, or by induction of death receptor-mediated apoptosis. Furthermore, they secrete a variety of cytokines and chemokines that promote the adaptive immune system to activate macrophages and lymphocytes [1, 2]. The percentage and/or absolute count of NK cells increase with age, whereas NK cell cytotoxicity decreases with age [3, 4].

NK cells are an important component in the early stages of anticancer defense. The high cytotoxic activity of NK cells is associated with reduced cancer risk [5]. However, tumors can escape immune surveillance by various mechanisms, which induces reduced immunogenicity and leads to upregulation of inhibitory receptors on NK cells or downregulation of the ligands on tumor cells for NK cell activating receptors [1, 2]. Previously, increased expression of the inhibitory NKG2A receptor was observed in patients with renal cell carcinoma, resulting in decreased NK cell activity (NKA) [6]. Patients with prostate, gastrointestinal, or colon cancer showed reduced NK cell numbers and activity, with a high level of T-regulatory cells [7]. In hematological malignancies, de-

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Received: July 20, 2017
Revision received: November 29, 2017
Accepted: November 29, 2017

This article is available from http://www.labmedonline.org

fective NK functions have been described, and the characteristics and mechanisms of impaired NKA are under investigation [8-10]. NK cell infusion has been adopted to treat various malignancies as a form of cancer immunotherapy [11, 12].

To measure the cytotoxicity of NK cells, the ^{51}Cr-release assay is considered the gold standard method. However, it is dangerous because of the radioactive hazard, and involves a complex method. The expression of cell surface receptors and intracellular proteins associated with NKA or NK cell maturation can be measured by flow cytometry; however, flow cytometry is not a simple test for routine clinical testing.

Recently, a commercialized NKA assay kit (NK Vue assay, ATgen, Korea) was introduced. It is an easy to use quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kit that can be used to measure interferon-gamma (IFN-γ) secreted by *ex vivo*-stimulated NK cells in whole blood [13, 14].

The purpose of this study was to investigate the clinicopathological characteristics of NKA among various hematological malignancies at diagnosis and to evaluate their clinical value as a monitoring marker.

METHODS

1. Patients and samples

The study group included 111 patients diagnosed with hematological malignancies from February 2015 to August 2017. Among them, 18 patients had acute myeloid leukemia (AML, excluding acute promyelocytic leukemia), 31 had multiple myeloma (MM), and 62 had lymphoma (five Hodgkin lymphoma [HL] and 57 non-Hodgkin lymphoma [NHL], including 31 with diffuse large B cell lymphoma, 19 with other B cell lymphoma, and seven with T cell lymphoma). Serial assessment of NKA was performed in 63 patients (eight AML, 17 MM, and 38 lymphomas) during follow-up.

To compare NKA in hematological malignancy with those in a normal control group, 23 healthy subjects were recruited from our health examination center out of 51 subjects who had the results of NKA for the same period. All the subjects had the results of complete blood cell (CBC) analysis. Thirteen patients with a history of hypertension, diabetes mellitus, and/or dyslipidemia were excluded. Five patients were excluded because of a history of thyroid cancer, two for autoimmune disease, two for glaucoma, four for recent medication, one for hepatitis B virus infection, and one for anemia.

Response criteria from the recommendations of the International Working Group for Response Criteria [15] were applied for AML. The International Myeloma Working Group uniform response criteria [16] and the revised response criteria from the International Working Group 1999 [17] were applied for MM and malignant lymphoma assessment, respectively.

2. NK cell activity measurement

Whole blood was collected in a tube containing PROMOCA, an engineered recombinant cytokine. The origin of IFN-γ secretion after PROMOCA stimulation in whole blood is as follows: CD3-/CD56+ NK cells account for more than 50% of IFN-γ+ cells and CD3+ T cells and NKT cells for around 30% of IFN- γ+ cells [13]. After 24 hours of incubation at 37°C in a CO_2 chamber, the supernatant was collected and stored at –20°C until the IFN-γ secreted by the NK cells was measured using the ELISA method. All measurements were performed according to the manufacturer's instructions.

The normal reference interval was stated as ≥250 pg/mL by the manufacturer. The analytical measurement range (AMR) of the NK Vue kit is 40–2,000 pg/mL, as indicated by the manufacturer. Values outside of the AMR were regarded as extreme values: 40 pg/mL and 2,000 pg/mL.

3. Peripheral lymphocyte subset analysis

The peripheral lymphocyte subsets (CD3, CD4, CD8, CD19, and CD56/16) were investigated using monoclonal antibodies (BD Multitest 6-color TBNK, Becton Dickinson, San Jose, CA, USA) using 6-color flow cytometry analysis (FACSCanto II Flow Cytometer, Becton Dickinson). Peripheral blood NK cell numbers were determined using lymphocytes staining positive for CD56 and CD16, and negative for CD3. The reference intervals for NK cell percentage and number in our laboratory were 5–15% and 126–592/μL, respectively.

4. Statistical analysis

Using Analyse-it 4.65.2 (Analyse-it Software, Ltd., Leeds, UK), NKA was compared among the hematological malignancies at diagnosis using the Wilcoxon-Mann-Whitney test and post-hoc analysis. The correlations of NKA with lymphocyte subsets and the other parameters were assessed by the Pearson correlation coeffi-

https://doi.org/10.3343/lmo.2018.8.2.41

cient. The correlation coefficient was interpreted as follows: $r<0.30$, negligible correlation; $0.30 \leq r<0.50$, low correlation; $0.50 \leq r<0.70$, moderate correlation; $0.70 \leq r<0.90$, high correlation; and greater than 0.90, very high correlation [18]. $P<0.05$ was considered as the level of statistical significance.

RESULTS

1. Comparison of NK cell activity, and relative and absolute NK cell numbers of hematological malignancies at diagnosis

The demographic and laboratory features of patients at diagnosis and the normal controls are shown in Table 1. The median value of NKA was 202.80 pg/mL (range 40–2,000 pg/mL) in all 111 patients with hematological malignancies, whereas that of the normal control group was 1,891.00 pg/mL (range 412–2,000 pg/mL). Among them, NKA was significantly decreased in the AML group (median 47.05 pg/mL, range 40–2,000) compared with the lymphoma group (median 289.49 pg/mL, range 40–2,000, $P=0.0499$, Table 1, Fig. 1) and the normal control group ($P<0.0001$). Significantly lower NKA was observed in patients with MM ($P<0.0001$) and lymphoma ($P<0.0001$) compared with that in the controls. Of the 57 patients with lymphoma who had bone marrow examination, the 11 patients with bone marrow involvement with lymphoma showed lower NKA (median 78.47 pg/mL, range 40–1,217.20) compared with that in the 46 patients without bone marrow involvement (median 338.65 pg/mL, 40–2,000, $P=0.0566$); however, the difference was not statistically significant.

The white blood cell (WBC) count in lymphoma was higher than that in the controls ($P=0.0160$). The neutrophil count in AML was significantly lower than that in MM, lymphoma, and the controls ($P=0.0030$, $P=0.0006$, and $P=0.0135$, respectively), while the neutrophil counts in MM and lymphoma were significantly higher than those in the controls ($P=0.0158$ and $P=0.0008$, respectively). Lymphocyte numbers in patents with AML were sig-

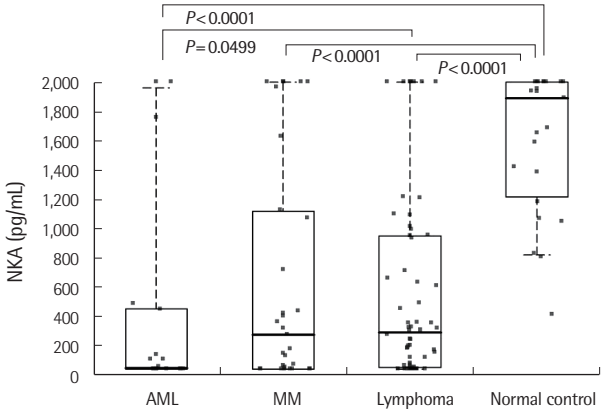

Fig. 1. Comparisons of the natural killer (NK) cell activity (NKA) among patients with hematological malignancies at diagnosis and controls. Boxes are inter-quartile ranges, horizontal bars are medians, and dotted lines are 10th and 90th percentiles.

Table 1. Demographic and laboratory features of patients with hematological malignancies at diagnosis

	AML (N=18)	MM (N=31)	Lymphoma (N=62)	Normal Control (N=23)	*P*
Age (year)	56.5 (34–92)	70.0 (40–89)	59.5 (17–90)	51.0 (37–59)	<0.0001
Sex ratio (Male:Female)	1.57:1	1.38:1	0.82:1	0.53:1	0.2317
WBC (/μL)	3,225 (770–133,710)	5,740 (1,470–13,550)	6,585 (1,840–21,000)	4,950 (2,590–8,940)	0.0930
Neutrophil count (/μL)	480 (0–11,524)	3,796 (610–8,640)	3,874 (930–10,650)	2,690 (1,060–3,800)	0.0001
Lymphocyte count (/μL)	1,137 (540–19,114)	1,539 (310–6,998)	1,698 (190–19,320)	2,052 (1,128–4,657)	0.0756
Neutrophil / Lymphocyte (ratio)	0.31 (0.00–6.00)	2.17 (0.10–17.79)	2.49 (0.06–92.95)	1.24 (0.67–2.93)	<0.0001
Lymphocyte percentage (%)	41.2 (8.0–83.1)	30.5 (7.1–87.8)	25.9 (2.2–92.0)	37.6 (24.0–52.1)	0.0007
NK cell activity (pg/mL)*	47.05 (40–2,000)	275.00 (40–2,000)	289.49 (40–2,000)	1,891.00 (412–2,000)	0.1595
NK cell (CD3-/CD56+/16+) percentage (%)	11.7 (2.5–35.6)	18.9 (5.3–66.2)	15.2 (2.3–48.2)	NT	0.1276
NK cell (CD3-/CD56+/16+) count (/μL)	206 (31–4,102)	317 (48–1,489)	222 (9–1,503)	NT	0.2127
CD3+ cell count (/μL)	1,195 (461–10,464)	1,144 (215–6,353)	1,114 (142–3,818)	NT	0.5369
CD3+/CD4+ cell count (/μL)	820 (261–5,857)	550 (95–5,891)	571 (55–2,148)	NT	0.2753
CD3+/CD8+ cell count (/μL)	441 (106–4,136)	384 (7–1,436)	325 (54–1,574)	NT	0.4294
CD19+ cell count (/μL)	169 (2–4,266)	129 (11–436)	161 (6–13,955)	NT	0.6061
CRP (mg/dL)	2.00 (0.08–25.61)	0.81 (0.04–9.64)	0.51 (0.04–15.19)	NT	0.0985

Except for sex ratios, all values are medians (range).
*Values outside of the analytical measurement range were regarded as extreme values: 40 pg/mL and 2,000 pg/mL
Abbreviation: NT, not tested.

nificantly lower than those in all other groups. The neutrophil to lymphocyte (N/L) ratio showed the same trends as the neutrophil count. Lymphocyte percentages in AML and controls were higher than those in MM and lymphoma (P=0.0007, Table 1.).

The three groups with hematological malignancies did not show significant differences in NK cell percentage, NK cell count, and all the other lymphocyte subsets.

2. Correlations between NK cell activity and WBC parameters, including NK cell number and lymphocyte subset

NKA did not correlate with NK cell percentage and NK cell count in the hematological malignancies (Table 2). No significant associations were observed in the regression analysis between NKA and absolute counts of CD3+, CD3+/CD4+, CD3+/CD8+, and CD19+ cells. There was no significant association between NKA and WBC count, neutrophil count, lymphocyte count, N/L ratio, or C-reactive protein (CRP). Interestingly, NKA had a low positive correlation with the lymphocyte percentage (r=0.373, P=0.0386) and a low negative correlation with the neutrophil count (r=–0.482, P=0.0060) in patients with MM.

3. Serial NK cell activity during follow-up

NKA was serially measured in 62 patients as a monitoring marker of immunological status during the follow-up period (from 2 to 27 months) (Fig. 2). Patients with relapsed disease or progressive disease are analyzed. NKA was stable in patients with complete remission status or partial response status (AML case 7; MM cases 3, 11, and 12; and lymphoma cases 34 and 37), but decreased at the time of or before relapse and disease progression in some patients (AML cases 1, 7, and 8; MM cases 1, 12, 13, and 16; and lymphoma cases 1, 6, 18, 26, 34, 35, 36, and 37).

In four patients (MM cases 3 and 13, and lymphoma cases 26 and 35), NKA was decreased before relapse but unexpectedly increased at the time of relapse. One patient with MM patient (MM case 11) had a high NKA (1,363 pg/mL) at the time of reappearance of monoclonal protein in urine without serum M-protein (suggesting relapse); however, on the next visit 3 months later, the patient showed decreased NKA (86 pg/mL) with conspicuous disease progression and was shown to have a serum M-protein level of 0.58 g/dL. Likewise, one lymphoma patient (lymphoma case 38) had high NKA at the time of relapsed disease and significantly low NKA afterwards.

NKA increased after autologous or allogeneic peripheral blood stem cell transplantation (PBSCT) compared with that of before stem cell transplantation (SCT) (AML case 1; MM cases 12 and 13; and lymphoma cases 34 and 35) and achieved complete remission. One patient with MM (MM case 11) sustained the complete response after autologous PBSCT but later showed decreased NKA (86 pg/mL), in accordance with increased urine level of free light chain (from 25 to 95 mg/L). One patient (lymphoma case 36) continued to have a low NKA (<40 pg/mL), even after autologous PBSCT; this patient relapsed after 2 months.

Some patients showed consistently low or normal NKA levels,

Table 2. Correlations of NK cell activity with WBC parameters including NK cell numbers and lymphocyte subsets in patients with hematological malignancies at diagnosis

	AML (N=18)		MM (N=31)		Lymphoma (N=62)		Normal control (N=23)	
	r	*P*	r	*P*	r	*P*	r	*P*
WBC count	–0.310	NS	–0.231	NS	–0.103	NS	0.325	NS
N/L ratio	–0.005	NS	–0.307	NS	–0.150	NS	0.091	NS
ANC	–0.229	NS	–0.482	0.0060	–0.283	0.0300	0.288	NS
Lymphocyte count	–0.234	NS	0.197	NS	0.148	NS	0.302	NS
Lymphocyte percentage	0.209	NS	0.373	0.0386	0.259	0.0421	0.040	NS
CRP	–0.264	NS	–0.310	NS	–0.337	0.0218	NT	NT
NK cell (CD3-/CD56+/16+ cell) count	–0.266	NS	–0.059	NS	0.172	NS	NT	NT
NK cell (CD3-/CD56+/16+ cell) percentage	–0.284	NS	–0.201	NS	–0.025	NS	NT	NT
CD3+ cell count	–0.288	NS	0.249	NS	0.188	NS	NT	NT
CD3+/CD4+ cell count	–0.285	NS	0.288	NS	0.224	NS	NT	NT
CD3+/CD8+ cell count	–0.266	NS	–0.005	NS	0.086	NS	NT	NT
CD19+ cell count	–0.298	NS	–0.100	NS	0.108	NS	NT	NT

Abbreviations: WBC, white blood cell; ANC, absolute neutrophil count; NS, not significant; N/L ratio, neutrophil to lymphocyte ratio; NT, not tested; CRP, C-reactive protein.

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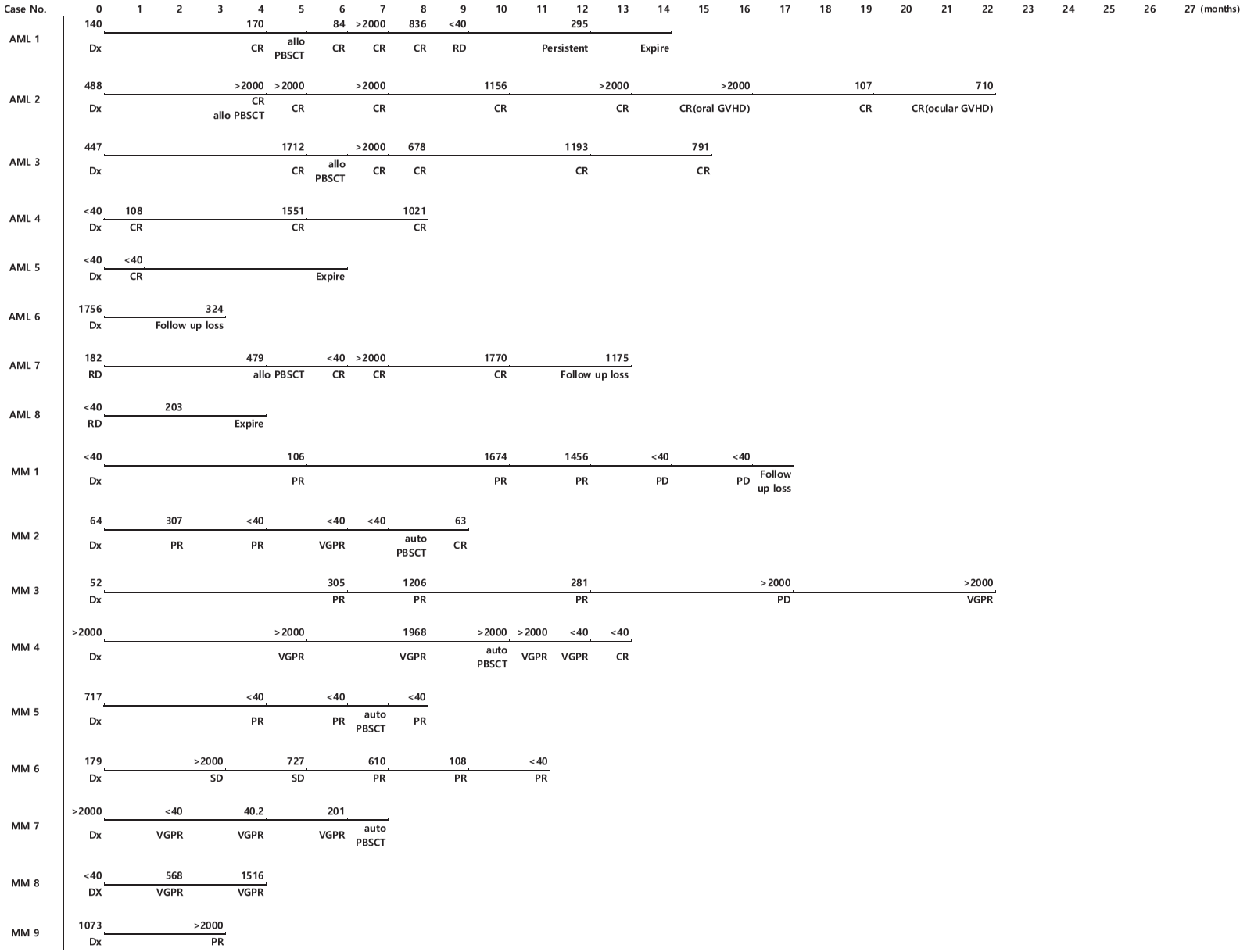

Fig. 2. Serial analysis of natural killer (NK) cell activity (NKA) during follow-up in patients with hematological malignancies. NKA is presented as pg/mL.
Abbreviations: Allo-PBSCT, allogeneic peripheral blood stem cell transplantation; Auto-PBSCT, autologous peripheral blood stem cell transplantation; CR, complete response; Dx, diagnosis; PD, progressive disease; PR, partial response; RD, relapsed disease; SD, stable disease.
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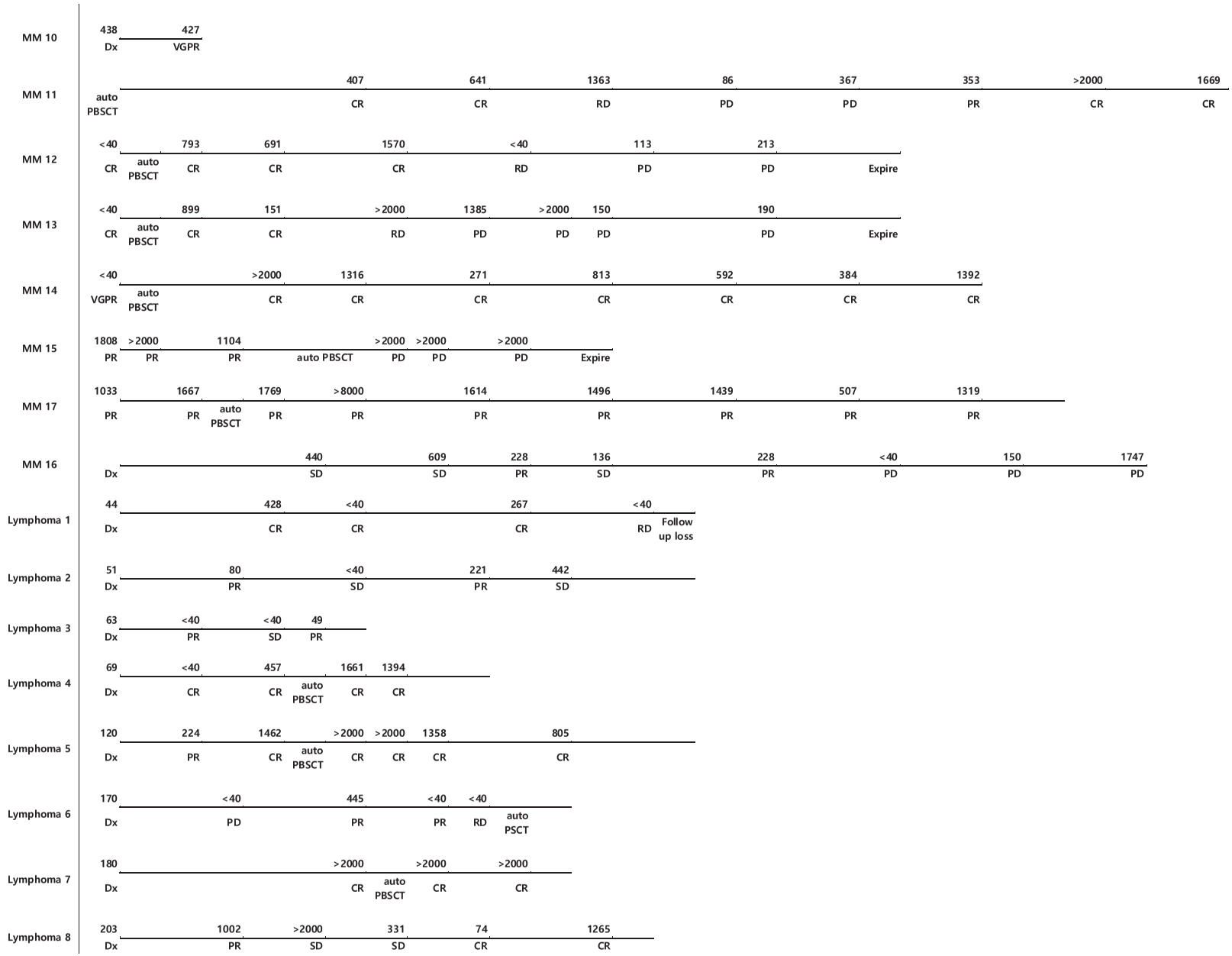

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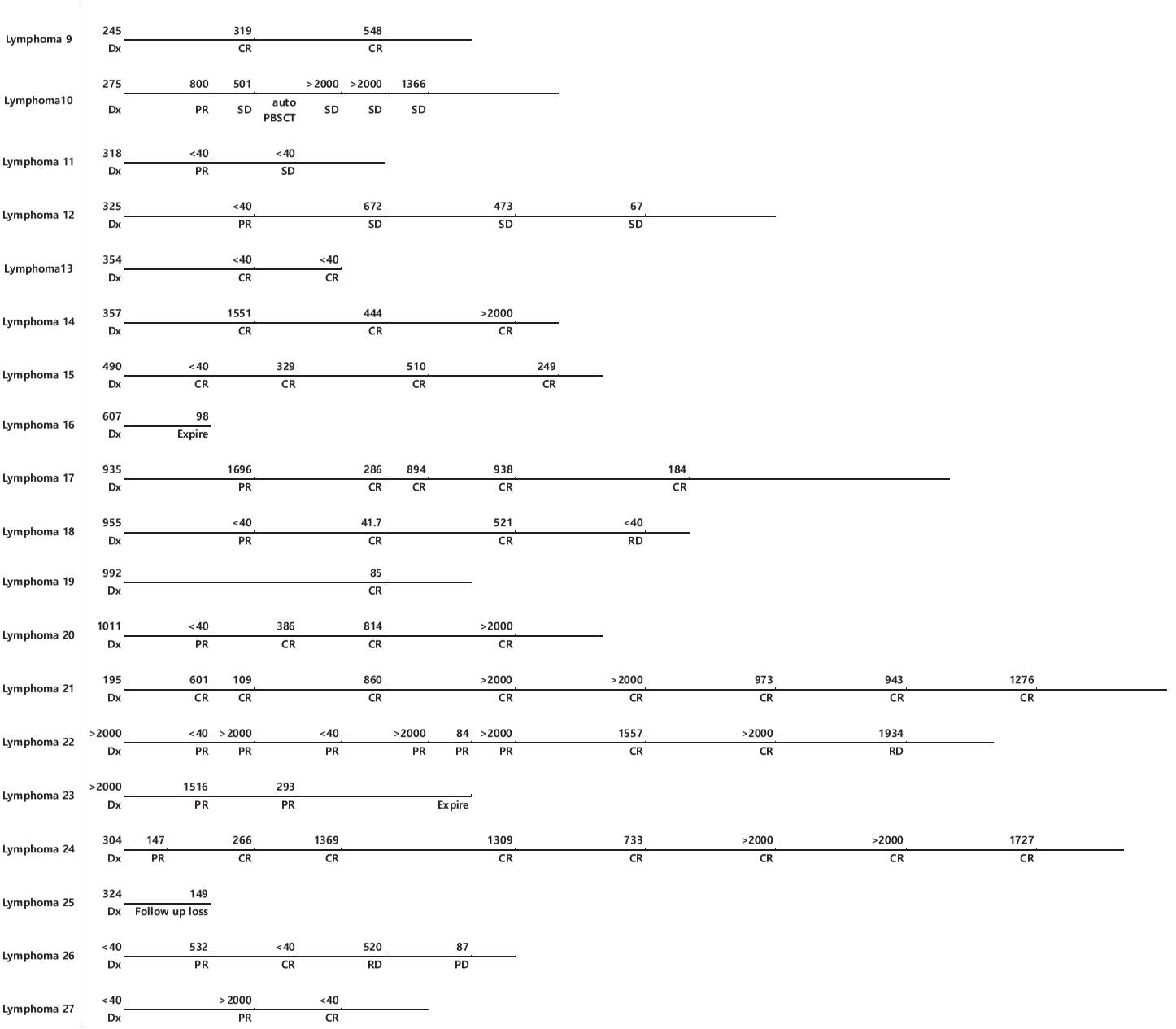

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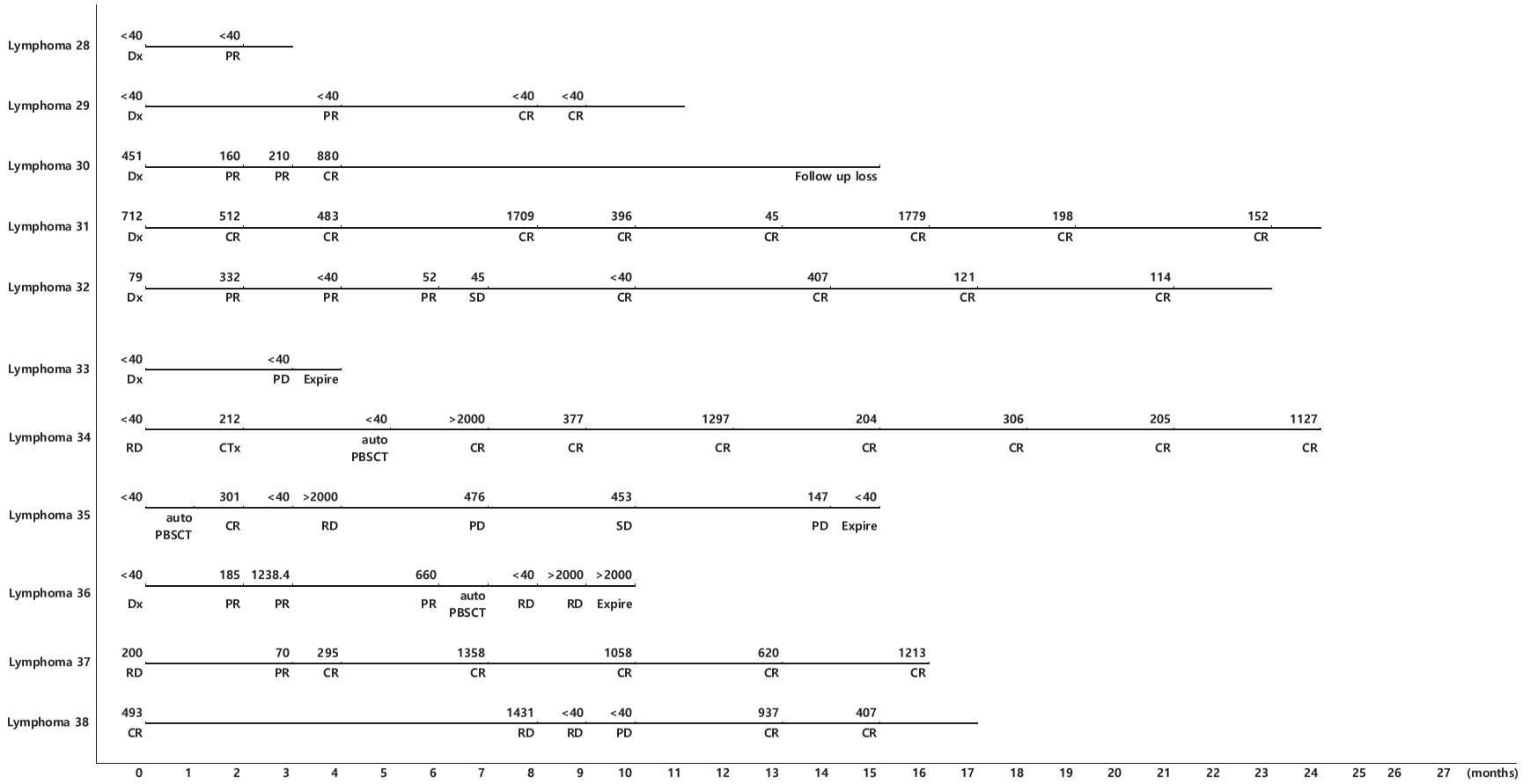

Fig. 2. Continued.

irrespective of disease course.

DISCUSSION

This study showed that NKA was significantly decreased in patients with hematological malignancies at diagnosis compared with that in the normal controls. Serial changes in NKA correlated with disease progression. NKA did not correlate with NK cell percentage and NK cell count.

NKA is a well-conserved characteristic in an individual [19]. There have been reported defects in NKA in hematological malignancies [8-10, 20]; however, it is not clear whether the decreased NKA in patients with hematological malignancies is the cause of cancer development or a result of it. The mechanisms of defective NKA could be quantitative (a decreased number of NK cells) or qualitative (increased expression of inhibitory receptors, decreased activation signaling, impaired NK cell differentiation signaling, or impaired cytokine production) [20]. A previous study revealed that a quantitative NK cell deficiency was found in myelodysplastic syndrome, whereas NKA was defective in polycythemia vera and chronic lymphocytic leukemia, even though the numbers of NK cells were increased [20]. Another study also reported qualitative defects of NKA in MM [10]. NK cell numbers were not changed or increased in MM; however, NKA decreased, as shown by altered patterns of activating and inhibitory receptors [10]. In patients with AML, a qualitative NKA defect was associated with reduced expression of certain activating NK receptors and decreased IFN-γ production [21]. In agreement with those studies, our study confirmed the qualitative impairment in NKA in hematological malignancies. As shown in Table 2, there was no correlation between NKA and NK cell percentage and NK cell count. Therefore, to evaluate NK cells quantitatively and qualitatively, both NKA and NK cell number should be measured.

The median NKA for lymphoma in our study was 289.49 pg/mL and was higher compared with that in the AML group (Table 1). Lymphoma is a malignant neoplasm of B or T cells from the lymphatic system that provokes a host immune response. NK cell function can be influenced primarily by the anatomical site of the tumor clone. One study showed that NK cell function is markedly impaired in patients with chronic lymphocytic leukemia (CLL), but is preserved in patients with small lymphocytic lymphoma (SLL) [22]. SLL is characterized by lymphadenopathy and/or splenomegaly in the absence of a peripheral lymphocytosis, whereas B-CLL is defined by the presence of tumor cells in the blood. B-CLL tumor cells produce considerable amounts of transforming growth factor beta 1 (TGF-β1), and chronic exposure to high levels of TGF-β of CLL tumor cells within the circulation can result in decreased expression of NKG2D (NKG2-D-Activating NK Receptor) and impaired NKA mechanisms. Therefore, the difference in NKA between AML and lymphoma patients could be partially caused by the tissue distribution of tumor cells. The finding that the NKA of lymphoma with bone marrow involvement showed a borderline significant difference ($P=0.0566$) from that of non-BM involvement of lymphoma, supported our suggestion.

In non-Hodgkin's lymphoma (NHL) with unfavorable histology, NKA was decreased [23]. One study showed that NK cells showed activated phenotypes at early stages by reducing MHC class I expression of tumor cells; however, in later stages, tumor cells re express MHC class I and lose natural killer group 2D ligands (NKG2D-L), which results in a decreased NKA [24]. Thus, NK cell effector functions can be progressively exhausted by increasing tumor load at the later stages.

In this study, the serial changes in NKA correlated with the clinical course. NKA was stable during complete remission status, but decreased at the time of, or before, relapse and disease progression. NKA has been proposed as an immunological surrogate marker in patients with hematological malignancies and as a predictor of the effect of anticancer therapy [9, 10]. In AML, NK cytotoxicity and effector cytokine function were restored following induction chemotherapy [25]. AML patients with defective NK cells had a significantly higher risk of relapse [25]. MM patients showed a decreased NKA with advanced clinical stage, and patients with a high NKA after chemotherapy showed better survival than patients with a low NKA [26]. Interestingly, lenalidomide and pomalidomide for MM treatment stimulate NK cells [27].

Some studies highlighted the ability of NK cells to exert potent anti-leukemic effects and to reduce relapse in patients after autologous or allogeneic SCT [2, 20, 28, 29]. In the present study, NKA of patients increased after SCT compared with that before SCT; these patients achieved complete remission. However, a decreased NKA was observed with relapse. One study showed that, during the first few months post-SCT, NK cells were the predominant circulating lymphoid cell subset with the potential to control disease relapse [2]. Another study demonstrated that a low absolute NK cell

count at 60 days post-transplant was independently associated with relapse and death among patients receiving reduced intensity conditioning, and there was no significant association between the absolute NK cell count and graft-versus-host disease [28].

In conclusion, this study showed that NKA was significantly decreased in patients with AML, MM, and lymphoma. The serial changes in NKA correlated with the clinical course. NKA could be useful to evaluate the immunological status in hematological malignancies at diagnosis and during follow-up. However, these findings must be verified in further studies to monitor markers of immune status and clinical correlations in a larger cohort.

요 약

배경: 자연살해세포는 일차 면역 반응에서 핵심적인 역할을 하며, 항암 방어기전의 주요 구성원이다. 이 연구에서는 다양한 혈액 종양에서 자연살해세포의 활성도와 관련된 임상병리학적 특성과 모니터링 표지자로서 임상적 가치를 알아보고자 하였다.

방법: 새로이 혈액종양을 진단받은 총 111명의 환자를 대상으로 하였는데 18명의 급성골수성백혈병 환자, 31명의 다발골수종 환자, 그리고 62명의 림프종 환자가 포함되었다. 정상 대조군은 건강검진센터에서 23명을 모집하였다. 자연살해세포활성도는 전혈 검체를 이용하여 체외에서 자극된 자연살해세포가 분비하는 인터페론감마를 측정하는 효소면역법 검사를 이용하였다.

결과: 111명 환자의 자연살해세포활성도 중앙값은 202.80 pg/mL (범위 40–2,000)이었다. 자연살해세포활성도는 급성골수성백혈병 환자(중앙값 47.05 pg/mL, 40–2,000, $P<0.0001$), 다발골수종 환자(275.00 pg/mL, 40–2,000, $P<0.0001$)와 림프종 환자(289.49 pg/mL, 40–2,000, $P=0.0073$)에서 정상대조군(1,891 pg/mL, 412–2,000)보다 유의하게 낮은 결과를 보였다. 자연살해세포활성도는 급성골수성백혈병 환자와 림프종 환자 간에 차이가 있었다($P=0.0499$). 자연살해세포활성도는 혈액종양질환이 있는 세 군 모두에서 자연살해세포수와 상관관계를 보이지 않았다.

결론: 자연살해세포의 활성도를 측정하는 것이 혈액종양 환자의 진단이나 추적 관찰 동안 환자의 면역상태를 평가하는 데 유용할 것으로 생각된다.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

ACKNOWLEDGEMENTS

This study was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (NRF-2012-R1A1A2044138).

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