Jpn. J. Cancer Res. 87, 930–937, September 1996

p53 Mutation in B-Cell Lymphoid Neoplasms with Reference to Oncogene Rearrangements Associated with Chromosomal Translocations

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We investigated mutations of the *p53* tumor suppressor gene in B-cell lymphoid neoplasms with reference to oncogene rearrangements associated with specific chromosomal translocations. These included 15 patients with a *BCL1/PRAD1* gene rearrangement and/or *PRAD1* overexpression, 45 with a *BCL2* rearrangement, 2 with a *BCL3* rearrangement, 24 with a *BCL6* rearrangement, and 6 with both *BCL2* and *BCL6* rearrangements. Thirty-six patients lacked detectable oncogene rearrangements. Genomic DNA was isolated from involved tissues or leukemic cells obtained at diagnosis and/or at relapse, and established cell lines. Polymerase chain reaction-mediated single-strand conformation polymorphism analysis and direct sequencing were performed to analyze abnormalities of the *p53* gene. We detected *p53* gene alterations in 18 of 128 patients, representing 21 of the total 151 materials analyzed. In the total of 66 patients with an oncogene rearrangement studied at diagnosis, only one had a mutation; however, 6 of 37 patients studied at relapse showed *p53* mutations. Sequential analysis revealed that the *p53* mutation was closely associated with transformation from follicular lymphoma to large cell lymphoma, exclusively in *BCL2*-positive lymphoma cases. Two of 13 mutations observed in oncogene rearrangement-positive cases and cell lines were transitions at CpG dinucleotides. In contrast, the relationship between *p53* mutations and clinical behavior in oncogene rearrangement-negative cases was variable; 5 patients including one with indolent follicular lymphoma were positive for *p53* mutation at initial presentation, and 2 of the 5 showed prolonged disease-free survival. Our findings suggest that *p53* alteration exhibits diverse functions in the development and progression of B-cell tumors related to the presence or absence of oncogene rearrangement, and that chemotherapy-related influences may be involved in the occurrence of progression-associated *p53* mutations.

Key words: *p53* mutation — PCR-SSCP — B-Cell lymphoid neoplasm — Oncogene rearrangement — Chromosome translocation

Human lymphoid neoplasms, including non-Hodgkin's lymphoma and lymphocytic leukemia, represent multiple diseases with diverse morphological and clinical features. For many years, pathological classification of lymphoma has been the focus of much discussion; immunohistochemistry and flow cytometry in addition to routine histopathology have provided much information regarding the cellular origin of lymphomas. Cytogenetic analysis is an independent approach which can be used to discriminate between distinct clinicopathologic subtypes within the generic group of lymphoid neoplasms. Studies of lymphomas have shown that 95–100% of non-Hodgkin's lymphomas exhibit chromosomal abnormalities,[1] and that some of the reciprocal chromosomal translocations are closely correlated with specific histological and immunological phenotypes. These observations suggest that lymphoid neoplasms can be divided into several subgroups according to individual primary translocation, and lymphomas in each subgroup show characteristic progression not only in clinical presentation, but also in additional genetic abnormalities.[2,3]

Recently developed molecular genetic techniques have demonstrated that oncogenes which are located at the breakpoints of nonrandom translocations play an integral role in the development of the lymphoid neoplasms. By using DNA probes from immunoglobulin genes, *BCL1/PRAD1*,[4,5] *BCL2*,[6] *BCL3*[7] and *BCL6*[8] oncogenes have been isolated. These oncogenes are juxtaposed with immunoglobulin gene loci or other as yet uncharacterized chromosomal loci, leading to transcriptional deregulation; the deregulated genes act dominantly in the development of lymphoid neoplasms.

The *p53* gene is a tumor suppressor gene which is affected in a wide range of human cancers including lymphoid neoplasms.[9–12] The most frequent mechanism by which the wild-type *p53* is inactivated is allelic loss of chromosome 17p, where the *p53* gene is located, followed by point mutation in the remaining allele. The *p53* prod-

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uct encoded by the mutated *p53* allele is inactive for cell growth arrest. Many studies of the *p53* alteration in hematological cancers have shown that *p53* alteration participates in the development and progression of a wide variety of these neoplasms. In follicular lymphomas, the *p53* mutation is frequently observed in lymphoma tissue showing histological transformation to large cell lymphoma.[13, 14]

It is widely accepted that many genetic lesions are accumulated in established human neoplasms. As described above, each subgroup of B-cell neoplasm associated with specific chromosomal translocation shows distinctive clinicopathological characteristics. Thus, it is possible that additional molecular aberrations play a role in the diversity of B-cell tumors. The aim of this study was to determine to what extent the *p53* alterations are correlated with oncogene rearrangements resulting from nonrandom translocation in B-cell lymphoid neoplasm.

MATERIALS AND METHODS

Patients and cell lines We studied 151 materials obtained from 128 patients with B-cell lymphoid neoplasms, including 95 clinical samples obtained at diagnosis, 47 at relapse and 9 established cell lines. Two or more materials were available in 19 patients, and 30 patients were first studied at relapse. The patients were admitted to Kyoto University Hospital and related hospitals between 1983 and 1994. FL-18, FL-218, FL-318 cell lines carried a t(14;18)(q32;q21) translocation, and HBL-2 cell line had a t(11;14)(q13;q32), as reported previously.[15, 16] The characteristics of FL-418 and FL-518 lines, which also bear a t(14;18), will be reported elsewhere.

All materials studied were subjected to surface immunophenotyping as well as gene rearrangement analysis using probes for the immunoglobulin heavy chain gene, to determine the B-cell origin of the neoplastic cells. Histological classification of non-Hodgkin's lymphomas was performed according to the International Working Formulation for Clinical Usage[17]; and newly identified disease entities,[18] which do not fit well to WF were classified independently.

Southern and Northern blot hybridization, and DNA probes High-molecular-weight genomic DNA extracted from tissues or cells was digested with appropriate restriction enzymes and electrophoresed through 0.8% agarose gels. Extraction and electrophoresis of RNA were performed as described previously.[15] DNA and RNA were transferred onto nylon membrane filters (GeneScreen Plus, NEN Research Products, Boston, MA), and hybridized with probes labeled with [α-^{32}P]-dCTP (3000 Ci/mmol, Amersham Japan, Tokyo) using a random labeling system. Hybridization and washing conditions were as recommended by the manufacturer. DNA probes were as follows: pRH11 for the major translocation cluster (MTC) region of the *BCL1* locus[4] and partial *PRAD1* cDNA fragment[5]; p18-4H (major breakpoint cluster region),[6] pFL-2 (minor breakpoint cluster region)[19] and pB16 (5′ fragment)[20] for the *BCL2* gene; pα1.4P and pα.5B for the *BCL3* gene[21]; F372 probe[22] representing the MTC region of the *BCL6* gene.

Polymerase chain reaction (PCR) amplification and single-strand conformation polymorphism (SSCP) analysis PCR amplification and subsequent SSCP analysis of the *p53* gene were carried out as described by Toguchida *et al.*,[23] with minor modifications. Briefly, 100 ng of genomic DNA was amplified by PCR in the presence of [α-^{32}P]dCTP (3000 Ci/mmol, Amersham Japan), using 6 sets of primers; 2 sets for exon 5 and one set for each of exons 6 through 9 of the *p53*. The PCR products were denatured and loaded onto 6% non-denaturing polyacrylamide gels in the presence or absence of 10% glycerol. The sequencing apparatus was cooled continuously by circulating water. After electrophoresis, the gels were dried and exposed to X-ray film at room temperature without an intensifying screen.

Direct DNA sequencing All samples showing aberrantly migrating bands on PCR-SSCP analysis were sequenced to identify mutations. The PCR products obtained as described above were purified using ultrafiltration kits (UltrafreeC3-TK; Millipore Japan, Tokyo), and then annealed with one of the two PCR primers which were end-labeled with [γ-^{32}P]ATP (Megalabel kit; Takara Shuzo, Kyoto). DNA sequences were determined by the dideoxy sequencing procedure using *Bca*BEST polymerase (*Bca*BEST Dideoxy Sequencing kit; Takara Shuzo), following the manufacturer's recommendations. Repeated sequencing with independent PCR was performed in all cases with mutations for verification.

Statistical analysis Correlations between oncogene rearrangements and *p53* mutations were analyzed with Fisher's exact test.

RESULTS

Rearrangement of oncogenes associated with chromosomal translocations The DNAs extracted from each material were probed with DNA fragments representing the *BCL1/PRAD1, BCL2, BCL3* and *BCL6* oncogenes, and gene rearrangements were determined by Southern blot hybridization. Of the 128 patients enrolled in this study, 12 patients had a *BCL1/PRAD1* rearrangement,[24] 45 had a *BCL2* rearrangement, 2 had a *BCL3* rearrangement, 24 had a *BCL6* rearrangement, and both *BCL2* and *BCL6* rearrangements were observed in 6 patients. Thirty-six patients lacked oncogene rearrangements detectable by the hybridization study. Three patients who had no detectable rearrangement within the *BCL1*-MTC

locus but showed abundant *PRAD1* transcript expression were included in the *BCL1/PRAD1* subgroup.[24]

Eleven of the total of 15 patients with the *BCL1/PRAD1* abnormality had mantle cell lymphoma.[24] Of 36 patients with the *BCL2* rearrangement at diagnosis, 26 had follicular small cleaved cell lymphoma and 5 had a large cell component in the follicle. Characterization of the two patients with B-cell chronic lymphocytic leukemia (B-CLL), showing the *BCL3* rearrangement, was described previously in detail.[25] The *BCL6* rearrangement was demonstrated in 7 patients with diffuse large cell lymphoma and in 5 patients whose lymphoma showed follicular proliferation.[26, 27]

In 19 patients, serial studies were performed, and histology of the involved tissue was seen to have changed in 7 patients. However, the DNA obtained at diagnosis as well as at relapse showed identical oncogene rearrangements, documenting the identical clonal origin of the neoplastic cells. No additional rearrangements were observed at relapse.

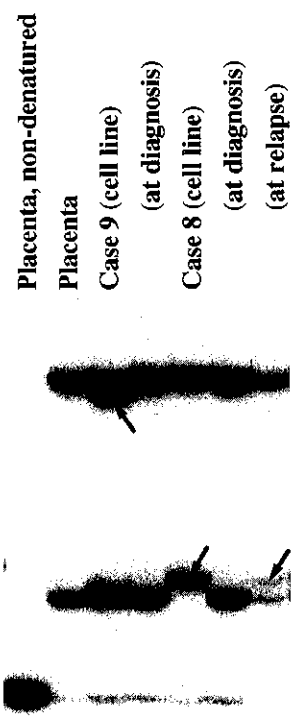

Fig. 1. Examples of PCR-SSCP analysis of *p53* mutations. DNA samples obtained from tumor cells and placental tissue were amplified by primer pairs for exon 8 of the *p53* gene. The PCR products were denatured and electrophoresed under non-denaturing conditions. Arrows indicate bands with shifted mobility representing mutation. Non-denatured PCR product from the placental DNA was electrophoresed as a reference. Cases 8 and 9 had follicular small cleaved cell lymphoma with the *BCL2* rearrangement. Both cases evolved into aggressive lymphoma composed of large cells at relapse, and a cell line was established from case 8.

PCR-SSCP analysis to detect *p53* alterations To determine alterations in the *p53* gene, exons 5 through 9 were amplified by PCR using primer pairs specific for each exon. The amplified DNA fragments were denatured and separated by electrophoresis under non-denaturing conditions. A representative autoradiogram showing altered electrophoretic mobility is shown in Fig. 1. PCR-SSCP analysis was performed on the total of 151 genomic DNAs; *p53* alterations were demonstrated in 21 DNAs obtained from 18 patients (Table I).

Among the total of 66 patients with an oncogene rearrangement studied at diagnosis, only one patient with a *BCL6* rearrangement had a mutation; however, 6 of 37 patients studied at relapse showed a *p53* mutation (1/66 versus 6/37; $P=0.0083$). In the *BCL2*-positive subgroup, *p53* mutations were detected only in relapsed cases (0/36 versus 4/16; $P=0.0067$), and 5 of 8 established cell lines carrying a *BCL2* rearrangement also carried a mutated *p53* gene. In contrast, 5 of 29 patients with no detectable oncogene rearrangement, including one with follicular large cell lymphoma, were positive for the *p53* mutation at initial presentation. There was a significant difference of the incidence of *p53* mutation in the primary tumor between the oncogene rearrangement-positive and -negative groups (1/66 versus 5/29; $P=0.0096$).

Nucleotide sequencing analysis of the *p53* mutation DNA fragments showing altered electrophoretic mobility on PCR-SSCP analysis were reamplified separately and the nucleotide sequences of the mutation were determined by direct sequencing. In case 8, a normal *p53* allele was also detected in tumor tissue obtained at relapse, probably reflecting contamination by normal reactive tissue, since the normal allele disappeared in the established cell line (Fig. 2). Alternative possibilities include that the tumor tissue was composed of two or more clones, of which one lacked the normal *p53* allele, and that the tumor cells had both a mutant and a normal allele, and deletion of the normal one occurred thereafter. In contrast, a germ line sequence in addition to a mutated nucleotide was detected in the established HBL-2, FL-218 and FL-318 cell lines, indicating heterozygosity of the lymphoma cells for the *p53* gene (Fig. 2).

Table II shows a summary of the results of sequencing analysis; the *p53* mutations were confirmed and characterized in all cases studied. A total of 20 nucleotide changes was found in 18 patients, and two independent mutations were detected in cases 2 and 10. Identical mutations were observed in parental samples and established cell lines (cases 5 and 8), indicating that the mutation did not occur during *in vitro* establishment. With the exception of one mutation in case 2, all nucleo-

Table I. Correlation of *p53* Mutation and Oncogene Rearrangements in B-Cell Neoplasms

Oncogene	*p53* mutation/ total patients studied	*p53* mutation/total materials studied		
		at diagnosis	at relapse	cell line
BCL1/PRAD1	2/15[a]	0/9	1/7	1/1
BCL2	7/45	0/36	4/16	5/7
BCL3	0/2[b]	0/2	NA	NA
BCL6	2/24	1/16	1/10	NA
BCL2 and *BCL6*	0/6[c]	0/3	0/4	0/1
No rearrangement	7/36	5/29	3/10	NA
Total	18/128	6/95	9/47	6/9

a) Three patients lacked rearrangement detectable by the MTC probe for the *BCL1* locus.[24]
b, c) Details were described in Refs. 25 and 26, respectively.
NA; not available for analysis.

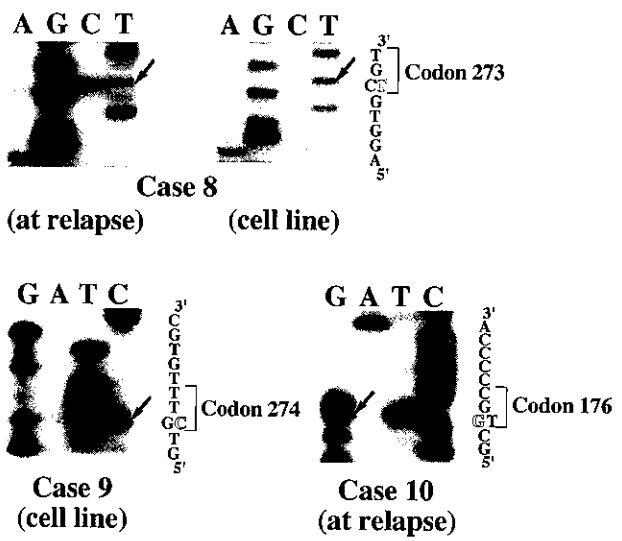

Fig. 2. Examples of the results of direct sequencing analysis of PCR products from the *p53* gene. Arrows indicate bands corresponding to base substitutions. Mutated nucleotides occurring at each codon are represented by outline letters. Case 10 had diffuse large cell lymphoma of the stomach associated with the *BCL6* rearrangement (case 3 in Ref. 26). Details of cases 8 and 9 are described in the legend to Fig. 1.

tide changes were single base pair substitutions resulting in changes in the coded amino acids. Eighteen of the 20 mutations were present within the highly conserved domains of the p53 protein. In cases 4 and 12, mutations were outside of the highly conserved domains; however, the amino acid residues altered in these cases are conserved among 4 mammalian species.[28]

Eight mutations were transitions in the form of G:C→A:T, and 7 were A:T→G:C, while the other 5 mutations were transversions. Transitions occurring at CpG dinucleotides were observed in 4 of the total of 20 mutations. With reference to the presence or absence of oncogene rearrangements, mutations at CpG dinucleotides seemed to occur less frequently in the oncogene rearrangement-positive group (2 of 13 mutations; 15.4%) than in the negative group (3 of 7 mutations; 42.9%), although this difference was not statistically significant.

Sequential analysis of the *p53* mutation Table III illustrates the *p53* mutations in the setting of clinical progression of each lymphoma case. Six lymphoma cell lines were established from each patient indicated. All the *BCL2*-positive patients showed clinical conversion to more aggressive lymphoma at relapse, and histological transformation from follicular small cleaved cell lymphoma to diffuse lymphoma composed of large cells was apparent in all cases but one. Sequential analysis of the *p53* mutation was performed in 4 *BCL2*-positive patients; *p53* mutation appeared at relapse in lymphoma tissue showing large cell morphology in 2 patients, and mutation was first identified in an established cell line in the other two.

In oncogene rearrangement-negative cases, the relationship between *p53* mutations and clinical presentation was variable. Case 13 with diffuse large cell lymphoma and case 15 with follicular large cell lymphoma responded to chemotherapy and showed prolonged disease-free survival. However, cases 16 and 18 were resistant to treatments and both showed a rapidly progressive course.

The present study included 8 established cell lines carrying a *BCL2* rearrangement. Five of these 8, listed in Table III, carried the t(14;18)(q32;q21) on cytogenetic analysis, and the breakage and rejoining with the immunoglobulin heavy chain gene occurred at the major breakpoint cluster region. In contrast, 2 of the other 3 cell lines lacking *p53* mutation showed rearrangement of *BCL2* at the 5′ region of the gene and the remaining one cell line at the minor cluster region (unpublished data). These observations raise the possibility that the particular site of the *BCL2* rearrangement may affect *p53* mutation.

Table II. Nucleotide Sequence Analysis of *p53* Mutations and Correlation with Oncogene Rearrangement

Oncogene Case No.	Status of materials	*p53* mutation			
		Exon	Codon	Nucleotide change	Amino acid change
BCL1/PRAD1					
1	at relapse	7	258	GAA→GGA	Glu→Gly
2	cell line	8	280	AGA→CGA	Arg→Arg
		8	281	GAC→GGC	Asp→Gly
BCL2					
3	cell line	5	127	TCC →TTC	Ser →Phe
4	at relapse	5	145	CTG →CAG	Leu→Gln
5	at relapse, cell line	5	176	TGC →TCC	Cys→Ser
6	cell line	7	248	CGG→CAG	Arg→Gln
7	at relapse	8	270	TTT →TCT	Phe→Ser
8	at relapse, cell line	8	273	CGT →TGT	Arg→Cys
9	cell line	8	274	GTT →CTT	Val →Leu
BCL6					
10	at relapse	5	176	TGC →GGC	Cys→Gly
		7	242	TGC →TGG	Cys→Trp
11	at diagnosis	8	285	GAG→AAG	Glu→Lys
No rearrangement					
12	at relapse	6	216	GTG→ATG	Val →Met
13	at diagnosis	7	236	TAC →TGC	Tyr→Cys
14	at diagnosis, relapse	7	246	ATG →GTG	Met→Val
15	at diagnosis	7	248	CGG→CAG	Arg→Gln
16	at diagnosis	7	258	GAA→AAA	Glu→Lys
17	at relapse	8	273	CGT →TGT	Arg→Cys
18	at diagnosis	8	282	CGG→GGG	Arg→Gly

DISCUSSION

We studied the relationship of *p53* mutation with oncogene rearrangement associated with specific chromosomal translocations in B-cell lymphoid neoplasms. As reported previously by others, the frequency of *p53* mutation increased with histological transformation from follicular lymphoma to large cell lymphoma as well as clinical disease progression, exclusively in *BCL2*-positive lymphoma cases.

We showed in a previous study[24] characteristics of lymphoma carrying the *BCL1/PRAD1* gene rearrangement. Patients with the rearrangement have advanced disease at initial presentation and show extensive dissemination to extra-nodal sites. These patients have a slowly progressive disease which is resistant to treatment; however, they do not display either acute conversion of the clinical manifestation or histological progression to more aggressive lymphoma. Indeed, the patient positive for *p53* mutation (case 1) consistently showed diffuse mixed cell morphology even in lymphoma tissues obtained postmortem. Thus, the significance of *p53* mutation in *BCL1/PRAD1*-positive cases is not as clear as that in *BCL2*-positive cases. However, it is likely that *p53* mutation was relevant to the emergence of chemotherapy-resistant clones, since the absence of wild-type p53 expression leads to a dramatic increase in cellular resistance to chemotherapy.[29]

Evaluation of the *p53* gene in B-CLL has been reported by several groups.[12] They showed that *p53* mutations appear to be more frequent in advanced CLL and in Richter's syndrome, suggesting that *p53* mutation is significantly correlated with disease progression in B-CLL.[30] The t(14;19)(q32;q13) translocation, resulting in *BCL3* rearrangement with the immunoglobulin heavy chain gene at the Cα constant locus, has been described in some patients with B-CLL showing prolymphocytoid transformation. As indicated previously,[25] leukemic cells from the two patients with *BCL3* rearrangement in the present study had immunoblastic morphology or prolymphocyte appearance, corresponding to the CLL/PL subtype according to the French-American-British group classification.[31] We thus proposed that CLL associated with *BCL3* rearrangement is distinctive within the general B-CLL category; patients with the rearrangement have a high propensity to show progression to a more aggressive leukemia. Sequential analysis of the leukemic cells will clarify whether *p53* mutation is associated with disease progression in CLL with deregulated *BCL3*.

Table III. Correlation of *p53* Mutation, Clinical Outcome and Oncogene Rearrangement

Oncogene Case No.	*p53* mutation[a]			Clinical outcome
	at diagnosis (histology[b])	at relapse (histology[b])	cell line (designation)	
BCL1/PRAD1				
1	NA (DMix)	wt/mut (DMix)	—	resistant to treatment
2	NA (DL)	—	wt/mut (HBL-2)	progressive disease
BCL2				
3	NA (FSC)	NA (DL)	mut (FL-18)	transformation
4	NA (unclassified)	mut (DL)	—	transformation
5	wt (FSC)	mut (DL)	mut (FL-518)	transformation
6	wt (FSC)	wt (DL)	wt/mut (FL-218)	transformation
7	NA (FSC)	wt/mut (DL)	—	transformation
8	wt (FSC)	wt/mut (DMix)	mut (FL-418)	transformation
9	wt (FSC)	wt (DL)	wt/mut (FL-318)	transformation
BCL6				
10	NA (DL)	wt/mut (DL)	—	relapse, progressive disease
11	wt/mut (DL)	NA (DL)	—	relapse, progressive disease
No rearrangement				
12	NA (FSC)	wt/mut (FL)	—	transformation
13	mut (DL)	—	—	prolonged remission
14	wt/mut (DL)	wt/mut (DL)	—	relapse, progressive disease
15	mut (FL)	—	—	prolonged remission
16	mut (DL)	—	—	progressive disease
17	NA	mut (DL)	—	relapse, progressive disease
18	mut (DL)	—	—	progressive disease

a) *p53* mutations; wt, wild type; mut, mutation.
b) Abbreviations for histological classification[17]; FSC, follicular small cleaved cell lymphoma; DMix, diffuse mixed cell lymphoma; DL, diffuse large cell lymphoma; unclassified, unclassified lymphoma.
NA, DNA was not available for analysis of the *p53* gene.

Offit *et al.*[32] have shown that patients with rearrangement of the *BCL6* gene have a favorable clinical outcome, although conflicting results have been presented by another group.[33] The relationship between *p53* mutation and *BCL6* rearrangement has not been reported. Although the number of cases studied is limited and any assessment must wait confirmation, two patients carrying both *BCL6* rearrangement and *p53* mutation showed poor responses to treatment and died from cancer cachexic syndrome. Thus, the implication of a relationship between *p53* mutation and poor clinical outcome could apply to *BCL6*-positive lymphoma.

The results of the present study demonstrated a clear difference in the occurrence of *p53* mutations between lymphomas characterized with translocation-associated oncogene rearrangement and those lacking any detectable rearrangement. Mutations at initial presentation occurred in the latter group more frequently than in the former, indicating that the mutation was not necessarily involved in disease progression. One possible explanation for the difference is that lymphomas associated with oncogene rearrangement, which acts dominantly in the development of B-cell neoplasms, may be clinically apparent at an early stage in the course of the disease; in contrast, lymphomas lacking deregulated oncogene resulting from chromosome translocation may require many genetic aberrations, including *p53* mutation, to be fully neoplastic. Another important observation in our study is that *p53* mutation does not necessarily seem to be a poor prognostic indicator, since *p53* mutation was demonstrated in a patient with follicular large cell lymphoma who has had a long disease-free survival. It has been shown that p53 appears to be required for normal B-cell differentiation[34] as well as apoptosis, and its lack thus leads to a prolonged lifespan of B-lymphocytes. Thus, although this is a very speculative hypothesis, it is possible that *p53* mutation in *BCL2*-negative follicular lymphoma is an equivalent of *BCL2* deregulation in the majority of cases with follicular lymphoma.

Mutations of the *p53* gene in human cancer can be found in about half of all cases and more than 90 percent of the *p53* gene mutations are missense mutations that change the identity of an amino acid.[9-12] Changing amino acids in this way can alter the conformation and increase the stability of the p53 protein, and can also indirectly alter the sequence-specific DNA binding and transcription factor activity of p53.[12] In leukemia and lymphoma cases, transitions at CpG dinucleotides, in the

form of C-to-T or G-to-A, constitute a major fraction of the *p53* point mutations.[11] This unusual mutability is attributed to the presence of the 5-methylcytosine residue found at these dinucleotides in the mammalian genome. However, in the present study, *p53* mutations observed in oncogene rearrangement-positive cases and established cell lines were relatively evenly distributed between G:C and A:T. Since all of such patients with *p53* mutations had been treated with cytotoxic drugs over several years, it is likely that chemotherapy-related effects, in addition to spontaneous mutation, may have played a significant role in the development of mutations.

In summary, this study has confirmed the close association of the *p53* mutation with disease progression in *BCL2*-positive lymphomas. However, *p53* mutation can occur in *de novo* cases with indolent follicular lymphoma lacking detectable oncogene rearrangement. These heterogeneous occurrences of *p53* mutation probably reflect diverse functions of the *p53* gene product in the development and progression of B-cell neoplasms, related to the presence or absence of oncogene rearrangement.

ACKNOWLEDGMENTS

We wish to thank the following doctors for providing clinical materials and information on the patients: Drs. Y. Ohno, H. Fujii, S. Doi, K. Nasu, T. Akaogi, K. Miyaoka, H. Konishi, T. Shimomura, Y. Konaka, Y. Izumi, N. Yasuda, N. Tomono, T. Suzuki, M. Seki, S. Watanabe, M. Abe and Y. Kobashi. This work was supported by Grants-in-Aid for Cancer Research from the Ministry of Health and Welfare (H4-1, 7-29), and from the Ministry of Education, Science, Sports and Culture of Japan (05151048, 07671196).

(Received April 10, 1996/Accepted June 12, 1996)

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