Research Article

DOI: 10.5505/tjh.2012.60362

The Frequency and Clinical Relevance of Multidrug Resistance Protein Expression in Patients with Lymphoma

Çoklu İlaç Direnci Protein İfadelerinin Lenfomalardaki Sıklık ve Klinik Önemi

Eren Gündüz[1], Murat Dinçer[2], Güniz Yıldız[1], Cengiz Bal[3], Zafer Gülbaş[4]

[1]*Eskişehir Osmangazi University, Department of Hematology, Eskişehir, Turkey*
[2]*Eskişehir Acıbadem Hospital, Medical Oncology Clinic, Eskişehir, Turkey*
[3]*Eskişehir Osmangazi University, Department of Biostatistics, Eskişehir, Turkey*
[4]*Anadolu Health Center in Affiliation with Johns Hopkins Medicine, Bone Marrow Transplantation Center, Kocaeli, Turkey*

Abstract

Objective: **Multidrug resistance is a cause of treatment failure in patients with malignant lymphoma; however, the frequency and clinical relevance of multidrug resistance protein expression are unclear. The present study aimed to investigate expression of the most common multidrug resistance proteins in a group of lymphoma patients.**

Material and Methods: **The study included 44 previously untreated lymphoma patients (non-Hodgkin's lymphoma [n = 21], non-malignant lymphadenopathy [n = 13], and Hodgkin's lymphoma [n = 10]). MDR1, MRP, and LRP expression was assessed via quantitative PCR of lymph node biopsy specimens.**

Results: **In the non-Hodgkin's lymphoma group MDR1 was positive in 23.8% (5/21) of the patients, MRP was positive in 57.14% (12/21), and LRP was positive in 90.47% (19/21). In the non-malignant lymphadenopathy group, MDR1 was positive in 46.15% (6/13) of the patients, MRP was positive in 84.61% (11/13), and LRP was positive in 100% (13/13). In the Hodgkin's lymphoma group MDR1 was positive in 50% (5/10) of the patients, MRP was positive in 50% (5/10), and LRP was positive in 80% (8/10). MDR1, MRP, and LRP expression did not differ between the 3 groups. Furthermore, MDR1, MRP, and LRP expression wasn't associated with tumor stage, response to first-line therapy, the erythrocyte sedimentation rate, or C reactive protein, beta 2 microglobulin, serum lactate dehydrogenase, and albumin levels. Additionally, survival time in the MDR1- and MRP-positive, and MDR1- and MRP-negative patients did not differ (comparison of LRP was not possible due to the small number of LRP-negative patients).**

Conclusion: **According to the present findings, future studies should investigate alternative pathways of multidrug resistance in order to arrive at a better understanding of treatment failure in lymphoma patients.**

Key Words: **Multidrug resistance, non-Hodgkin's lymphoma, Hodgkin's lymphoma, Survival**

Address for Correspondence: Zafer GÜLBAŞ, M.D.,
Anadolu Sağlık Merkezi, Kemik İliği Nakli Merkezi, Kocaeli, Turkey
Phone: +90 262 678 54 68 E-mail: zafer.gulbas@anadolusaglik.org

Received/*Geliş tarihi* : December 8, 2010
Accepted/*Kabul tarihi* : January 2, 2012

Özet

Amaç: Çoklu ilaç direnci malign lenfomalarda tedavi başarısızlığının nedenlerindendir. Fakat çoklu ilaç direnci proteinlerinin sıklığı ve klinik önemiyle ilgili çelişkiler mevcuttur. Biz bu çalışmada lenfomalı hastalarımızda en sık görülen çoklu ilaç direnci proteinlerinin ifadelerini araştırdık.

Gereç ve Yöntemler: Çalışmaya daha önce tedavi almamış 44 hasta (21 non Hodgkin lenfoma, 13 malign olmayan lenfadenopati, 10 Hodgkin lenfoma) alındı. MDR1, MRP ve LRP ifadeleri lenf nodu biyopsi örneklerinde kantitatif PCR ile değerlendirildi.

Bulgular: Non Hodgkin lenfomada MDR1 %23.8 (5/21), MRP %57.14 (12/21), LRP %90.47 (19/21) pozitifti. Malign olmayan lenfadenopatili hastalarda MDR1 %46.15 (6/13), MRP %84.61 (11/13), LRP %100 (13/13) pozitifti. Hodgkin lenfomada MDR1 %50 (5/10), MRP %50 (5/10), LRP %80 (8/10) pozitifti. MDR1, MRP ve LRP ifadeleri 3 grup arasında farklı değildi. İfadeler tümör evresi, eritrosit sedimantasyon hızı, C reaktif protein, beta 2 mikroglobulin, ilk sıra tedaviye yanıt, serum laktat dehidrogenaz ve albumin düzeyiyle ilişkili değildi. MDR1 ve MRP pozitif ve negatif hastaların yaşam süreleri arasında da fark bulamadık (LRP pozitif ve negatif hastalar arası karşılaştırma yapmak az hasta sayısı nedeniyle mümkün olmadı).

Sonuç: Verilerimize göre, bu grup hastalardaki tedavi başarısızlığını aydınlatmak için gelecekte yapılacak çalışmalar çoklu ilaç direncinin alternatif yolaklarına yönlendirilebilir.

Anahtar Sözcükler: Çoklu ilaç direnci, non Hodgkin lenfoma, Hodgkin lenfoma, Yaşam süresi

Introduction

Multidrug resistance (MDR) refers to the resistance of tumor cells to chemotherapeutic agents of varying chemical structure and mechanisms of action [1]. Numerous mechanisms are involved in drug resistance; among them, drug efflux transporters are one of the most intensively studied and most prevalent [2,3]. Common MDR proteins include permeability related glycoprotein (P-gp), multidrug resistance-associated protein (MRP), and lung resistance-related protein (LRP) [4,5]. P-gp, also referred to as P-170, is a product of the MDR1 gene and is an ATP-dependent pump capable of expelling drugs from cancer cells [6]. MRP is structurally similar to P-gp and is a member of the same transmembrane transporter superfamily [7]. LRP is a 110-kDa protein identified in a P-gp-negative MDR lung cancer cell line and functions as a major vault protein in humans [8].

Overexpression of MDR increases efflux of most lymphoma regimens from cells [9-11]. The predictive and prognostic value of MDR expression has previously been reported for multiple myeloma (MM) [12], acute myeloid leukemia (AML) [13], acute lymphoblastic leukemia (ALL) [14], and adult T-cell leukemia [15]. The MDR phenotype is also the major cause of treatment failure in patients with malignant lymphoma; however, findings regarding expression of the MDR1 gene/P-gp in malignant lymphoma patients are inconsistent [16-18].

Due to the non-clarity surrounding the frequency and clinical relevance of multidrug resistance protein expression, the present study aimed to investigate the expression of the most common MDR proteins in a group of previously untreated patients with lymphoma—specifically, whether or not these 3 multidrug resistance proteins were expressed and their impact on clinical outcome.

Materials and Methods

The study included 44 previously untreated patients that were diagnosed between 2005 and 2007. The patients were divided into 3 groups, according to pathology results. Group 1 included 21 patients diagnosed a diffuse large B-cell lymphoma (DLBCL) (n = 9), T-cell non-Hodgkin's lymphoma (NHL) (n = 8), and mantle cell lymphoma (MCL) (n = 4). Group 2 included 13 patients diagnosed as reactive lymphadenopathy (LAP) (n = 5), granulomatous inflammation (n = 5), dermatopathic LAP (n = 1), benign mixed tumor (n = 1) and Kikuchi's disease (n = 1). Group 3 included 10 patients diagnosed as Hodgkin's lymphoma (HL).

Survival time was defined as the period (months) from diagnosis to death or data analysis. MDR1, MRP, and LRP expression was assessed via quantitative PCR of lymph node biopsy specimens. Only biopsy specimens clearly proven to be malignant based on flow cytometric and pathological analysis were included in the study. Peripheral blood and lymph node biopsy specimens were obtained following provision of informed consent by the patients and approval of the study protocol by the Eskişehir Osmangazi University, School of Medicine Institutional Review Board.

The patients were treated with CVP, CHOP, Hyper-CVAD, IMVP16, DHAP, ESHAP, ABVD, and BEACOPP polychemotherapy. Patients with DLBCL and MCL also received rituximab. In all, 4 patients required radiotherapy and 4 other patients received additional peripheral stem cell transplantation (3 autologous and 1 allogeneic with reduced intensity conditioning). Response to chemotherapy was assessed according to standard criteria [19]. Tumor stage, the erythrocyte sedimentation rate, and C reactive protein, beta 2 microglobulin, serum LDH, and albumin levels were also recorded.

Detection of multidrug resistance

Lymph node biopsy specimens obtained in the surgical suite were immediately taken to the laboratory in Eppendorf tubes containing RPMI1640 medium. The specimens were preserved in liquid nitrogen at –80 °C and thawed at 4 °C before RNA isolation. An mRNA Isolation Kit II (Tissue) (Roche) was used to obtain RNA from the tissue samples using a MagNA Pure instrument. cDNA was obtained using a Transcriptor First Strand cDNA Synthesis Kit (Roche). MDR1, MRP, LRP, and beta actin primary probes from TIB MOLBIOL and Light Cycler Taqman Master reaction mix were used for quantitative PCR in a Roche Light Cycler instrument. As beta actin is present in all clinical samples, it was used as an intrinsic control. Quantitative MDR1, MRP, and LRP values were divided by the beta actin value, and the positive results were used for statistical analysis. We did not set a cut-off value and considered any level of expression as positive.

Statistical analysis

All statistical analyses were performed using SPSS (PASW) v.18.0 for Windows software. Distribution of the variables was determined using the Shapiro Wilks test. Parametric tests were used to analyze normally distributed data and non-parametric tests were used for data not normally distributed. The chi-square test was used for analysis of cross tables. Correlations between variables were determined by calculating Spearman's correlation coefficients. The independent samples t-test and ANOVA were used to compare group means of normally distributed variables. Tukey's post hoc test was used to determine different groups in ANOVA. The Kaplan Meier test was used to compare survival time between ≥2 groups. The log rank test was used to determine differences between mean survival times. $P < 0.05$ was considered statistically significant. Data are expressed as mean ± standard deviation (SD).

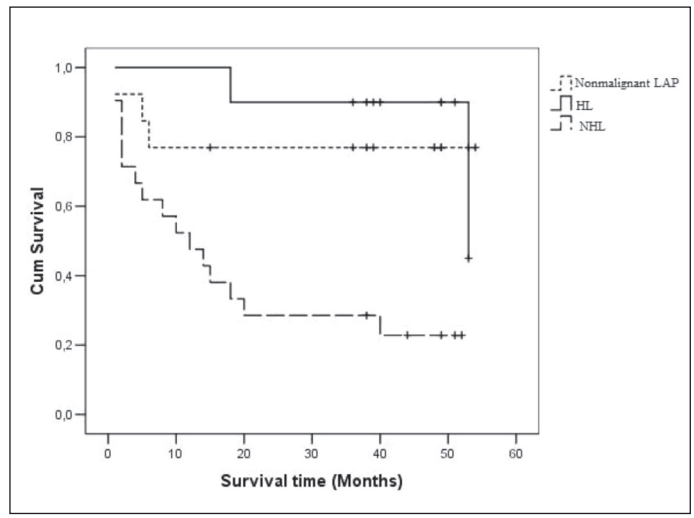

Figure 1: Figure. Survival time in the non-Hodgkin's lymphoma, non-malignant LAP, and Hodgkin's lymphoma groups.

Table 1: MDR1, MRP, and LRP positivity in the non-Hodgkin's lymphoma, non-malignant LAP, and Hodgkin's lymphoma groups.

	MDR1	MRP	LRP
NHL	23.8% (5/21)	57.14% (12/21)	90.47% (19/21)
Non-Malignant LAP	46.15% (6/13)	84.61 (11/13)	100% (13/13)
HL	50% (5/10)	50% (5/10)	80% (8/10)

Results

Mean age was 53.2 ± 17.5 years in the NHL patients (group 1), 41.7 ± 15.1 years in the non-malignant LAP patients (group 2), and 37.6 ± 13.7 years in the HL patients (group 3). NHL patients were older than HL patients ($P < 0.05$); the difference was not significant. Mean survival time was 19.69 ± 4.33 months in group 1, 42.46 ± 5.85 months in group 2, and 49.50 ± 4.69 months in group 3. NHL patients had shorter survival than HL patients ($P < 0.01$), but survival time did not differ between the reactive LAP and lymphoma patients ($P > 0.05$) (Figure).

MDR1, MRP, and LRP positivity in the 3 groups is shown in the Table. The frequency of MDR1, MRP, and LRP positivity was significantly different between the 3 groups ($P > 0.05$). While examining survival time in each group separately, comparison was not possible in some groups due to the small number of negative patients (MRP

and LRP in group 2, and LRP in groups 1 and 3). When the other groups were compared (MDR1 and MRP in group 1 and 3, and MDR1 in group 2) a significant difference in survival time between the MDR1- and MRP-positive, and the MDR1- and MRP-negative patients was not observed. In all, 5 patients in group 1 were positive for all 3 MDR proteins, 7 were positive for MRP and LRP, and 7 were positive only for LRP. In total, 6 patients in group 2 were positive for all 3 MDR proteins, 5 were positive for MRP and LRP, and 2 were positive only for LRP. Positivity for all 3 MDR proteins was observed in 3 patients in group 3 patients, whereas 1 patient was positive for MRP and LRP, 1 patient was positive only for MDR1, and 3 patients were positive only for LRP. There weren't any significant associations between MDR1, MRP, and LRP expression, and tumor stage, response to first-line therapy, the erythrocyte sedimentation rate, or C reactive protein, beta 2 microglobulin, serum LDH and serum albumin levels.

Discussion

In the present study expression of MDR1, MRP, and LRP was determined via quantitative real-time PCR (RT-PCR) in patients with lymphoma and non-malignant diseases, and the association between the expression of the 3 MDR proteins, and clinical and laboratory parameters was evaluated. To the best of our knowledge this is the first study to evaluate the frequency and clinical relevance of MDR proteins in patients with malignant lymphomas (both Hodgkin's and non-Hodgkin's) and non-malignant diseases. In contrast to AML, studies on lymphomas and MDR are few in number and have generally focused on P-gp expression, and most included a heterogeneous patient population. Furthermore, the methods used to determine MDR expression in such studies varied widely [20]. As such, comparison of the published data is difficult. Moreover, these studies included a small number of patients, as did the present study, and therefore definitive conclusions cannot be reached.

MDR1/P-gp expression in lymphomas has been previously examined. Liu et al. [21] reported that 41.7% of 24 B-cell lymphoma patients were MDR-1/P-gp-positive (based on RT-PCR) before treatment. Pileri et al. [22] reported that 44% of peripheral T-cell lymphoma patients and 40% of B-cell lymphoma patients were P-gp-positive before treatment. Findings regarding the clinical importance of MDR1/P-gp in lymphomas are inconsistent. MDR1/P-gp was reported to be predictive of a poor response to induction chemotherapy in 2 studies [22,23], but not in 2 other studies [24,25]. Overall, research shows that 2%-30% of lymphomas express P-gp immunohistochemically [22-24,26], increasing to 22%-50% when RNA-based analysis methods for detecting P-gp/MDR1 are used [24,25,27]. MDR1 expression in the present study was observed in 23.8% of non-Hodgkin's lymphoma patients and in 50% of Hodgkin's lymphoma patients; these percentages are similar to those previously reported. The present study's findings are also in agreement with studies that did observe a relationship between MDR1 expression [24,25] and poor response to induction chemotherapy.

Filipits et al. [28] reported that LRP was positive in 23% and MRP1 was positive in 44% of newly diagnosed DLBCL patients. LRP expression was associated with poor response to chemotherapy and shorter survival, which suggests that LRP is a clinically relevant drug resistance factor in DLBCL. A similar predictive and prognostic value of LRP expression was reported in patients with AML [15,29], ALL [30], MM [12], and advanced ovarian cancer [11]. Ohsawa et al. [31] reported that MRP1 was positive in 63% and LRP was positive in 68% of patients with nodal DLBCL. Huang et al. [32] observed MRP and LRP expression rates of 20.5% and 12.5%, respectively, in nasal NK/T-cell lymphoma patients. It is likely that the expression of MDR varies according to lymphoma subtype. In the present study expression of MRP and LRP was observed in 57.14% and 90.47% of NHL patients, respectively (LRP expression was higher than previously reported in Filipits [28], Oshawa [31] and Huang's [32] studies), versus MRP and LRP in 50% of HL patients, respectively.

MRP expression was not observed to play an important role in the mechanism of drug resistance associated with a poor clinical outcome in previously untreated NHL patients [33]. Filipits et al. [28] reported that MRP1 expression had no impact on the outcome of chemotherapy or survival in patients with DLBCL, and similar findings have been observed in refractory lymphoma patients in whom MRP expression was not determined via quantitative PCR [34]. Previous studies on AML [14,29], ALL [30], and advanced ovarian cancer [11] also failed to observe any predictive or prognostic significance of MRP1 expression. Additionally, in the present study MRP and LRP expressions had no correlation with response to induction chemotherapy or survival in lymphoma patients with mixed histopathology.

In the present study there weren't any significant correlations between MDR1, MRP, and LRP expression, and tumor stage, response to first-line therapy, the erythrocyte sedimentation rate, or C reactive protein, beta 2 microglobulin, and serum LDH and albumin levels in the NHL and HL patients. Mixed histopathology and differences in

treatment between the patients make it impossible to correlate the findings with clinical outcome, which is a limitation of the present study that warrants additional research. Anti-CD20 monoclonal antibody (rituximab) has become the standard therapy for aggressive NHL and has dramatically improved treatment outcome [35]. Recent laboratory-based evidence shows that rituximab interacts with P-gp [36]; unfortunately, due to mixed histopathology and the small number of patients (n = 13) in the present study, we were unable to examine that interaction.

Non-malignant tissues expressed MDR proteins in the present study and the frequency of expression was similar in all the lymphoma patients. In fact, normal lymphocytes were reported to express MDR1/P-gp [37], but Kang et al. [9] posited that contamination of tumor samples with T-lymphocytes and monocytes does not significantly increase the level of MDR1 expression. The similarity of MDR expression between lymphoma and reactive LAP patients observed in the present study may have been due to lack of a cut-off value and considering any level of expression as positive, or that 3 patients previously reported as reactive LAP were diagnosed as NHL following rebiopsies performed during follow-up.

In conclusion, MDR1, MRP, and LRP expression was not observed to influence overall survival in NHL and HL patients. The present findings indicate that additional studies should examine alternative pathways of MDR other than MDR1/P-gp, MRP and LRP expression (apoptosis etc.) to elucidate treatment failure in this group of patients. Furthermore, the frequencies of expression observed in the present study are noteworthy, as to the best of our knowledge this is the first study to report and compare these frequencies in HL patients and non-malignant patients.

Conflict of Interest Statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

References

1. Biedler JL, Riehm H. Cellular resistance to actinomycin D in Chinese hamster cells in vitro: cross-resistance, radioautographic and cytogenetic studies. Cancer Res 1970; 30: 1174-1184.
2. Borst P, Elferink RO. Mammalian ABC transporteri in health and disease. Annu Rev Biochem 2002; 71: 537-592.
3. Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: a role of ATP dependent transporters. Nat Rev Cancer 2002; 2: 48-58.
4. Ross DD. Novel mechanisms of drug resistance in leukemia. Leukemia 2000;14: 467-473.
5. Cho EY, Gong G, Khang SK, Kang YK, Huh J. Fine needle aspiration cytology of CD56-positive natural killer/T-cell lymphoma of soft tissue. Cancer 2002; 96: 344-350.
6. Shen DW, Cardarelli C, Hwang J, Cornwell M, Richert N, Ishii S, Pastan I, Gottesman MM. Multiple drug-resistant human KB carcinoma cells independently selected for high-level resistance to colchicine, adriamycin or vinblastine show changes in expression of specific proteins. J Biol Chem 1986; 261: 7762-7770.
7. Kruh GD, Chan A, Myers K, Gaughan K, Miki T, Aaronson SA. Expression complementary DNA library transfer establishes mrp as a multidrug resistance gene. Cancer Res 1994; 54: 1649-1652.
8. Scheper RJ, Broxterman HJ, Scheffer GL, Kaaijk P, Dalton WS, van Heijningen TH, van Kalken CK, Slovak ML, de Vries EG, van der Valk P, J.L.M. Meijer C, HM Pinedo. Overexpression of a M(r) 110,000 vesicular protein in non-P-glycoprotein- mediated multidrug resistance. Cancer Res 1993; 53: 1475-1479.
9. Kang YK, Zhan Z, Regis J, Alvarez M, Robey R, Meadows B, Dickstein B, Lee JS, Otsuki T, Stetler-Stevenson M, Jaffe ES, Solomon D, Wilson WH, Fojo A, Bates ES. Expression of mdr-1 in refractory lymphoma: quantitation by polymerase chain reaction and validation of assay. Blood 1995; 86: 1515-1524.
10. Cole SP, Bhardjaw G, Gerlach JH, Mackie JE, Grant CE, Almquist KC, Stewart AJ, Kurz EU, Duncan AM, Deeley RG. Overexpression of a transporter gene in a multidrug-resistant human lung cancer cell line. Science 1992; 258: 1650-1654.
11. Izquierdo MA, Shoemaker RH, Flens MJ, Scheffer GL, Wu L, Prather TR, Scheper RJ. Overlapping phenotypes of multidrug resistance among panels of human cancer cell lines. Int J Cancer 1996; 65: 230-237.
12. Filipits M, Drach J, Pohl G, Schuster J, Stranzl T, Ackermann J, Königsberg R, Kaufmann H, Gisslinger H, Huber H, Ludwig H, Pirker R. Expression of the lung resistance protein predicts poor outcome in patients with multiple myeloma. Clin Cancer Res 1999; 5: 2426-2430.
13. Filipits M, Pohl G, Stranzl T, Suchomel RW, Scheper RJ, Jäger U, Geissler K, Lechner K, Pirker R. Expression of the lung resistance protein predicts poor outcome in de novo acute myeloid leukemia. Blood 1998; 91: 1508-1513.

14. Borg AG, Burgess R, Green LM, Scheper RJ, Yin JA. Overexpression of lung-resistance protein and increased P-glycoprotein function in acute myeloid leukemia cells predict a poor response to chemotherapy and reduced patient survival. Br J Haematol 1998; 103: 1083-1091.
15. Yasunami T, Wang Y, Tsuji K, Takanashi M, Yamada Y, Motoji T. Multidrug resistance protein expression of adult T-cell leukemia/lymphoma. Leuk Res 2007; 31: 465-470.
16. Yuen AR, Sikic BI. Multidrug resistance in lymphomas. J Clin Oncol 1994; 12: 2453-2459.
17. Marie JP. P-glycoprotein in adult hematologic malignancies. Hematol Oncol Clin North Am 1995; 9: 239-249.
18. Sandor V, Wilson W, Fojo T, Bates SE. The role of MDR-1 in refractory lymphoma. Leuk Lymph 1997; 28: 23-31.
19. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, Lister TA, Vose J, Grillo-López A, Hagenbeek A, Cabanillas F, Klippensten D, Hiddemann W, Castellino R, Harris NL, Armitage JO, Carter W, Hoppe R, Canellos GP. Report of an International Workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 1999; 17: 1244-1253.
20. Saglam A, Hayran M, Uner AH. Immunohistochemical expression of multidrug resistance proteins in mature T/NK cell lymphomas. APMIS 2008; 116: 791-800.
21. Liu Q, Ohshima K, Kikuchi M. High expression of MDR-1 gene and P-glycoprotein in initial and re-biopsy specimens of relapsed B cell lymphoma. Histopathology 2001; 38: 209-216.
22. Pileri SA, Sabattini E, Falini B, Tazzari PL, Gherlinzoni F, Michieli MG, Damiani D, Zucchini L, Gobbi M, Tsuruo T. Immunohistochemical detection of multidrug transport protein P170 in human normal tissues and malignant lymphomas. Histopathology 1991; 19: 131-140.
23. Cheng AL, Su IJ, Chen YC, Lee TC, Wang CH. Expression of P-glycoprotein and anionic glutathione S-transferase in recurrent lymphomas: the possible role of Ebstein Barr virus immunophenotypes and other predisposing factors. J Clin Oncol 1993; 11: 109-115.
24. Niehans GA, Jaszcz W, Brunetto V, Perri RT, Gajl-Peczalska K, Wick MR, Tsuruo T, Bloomfield CD. Immunohistochemical identification of P-glycoprotein in previously untreated diffuse large cell and immunoblastic lymphomas. Cancer Res 1992; 52: 3768-3775.
25. Rodriguez C, Commes T, Robert J, Rossi JF. Expression of P-glycoprotein and anionic glutathione S-transferase genes in non Hodgkin's lymphomas. Leuk Res 1993; 17: 149-156.
26. Miller TP, Grogan TM, Dalton WS, Spier CM, Scheper RJ, Salmon SE. P-glycoprotein expression in malignant lymphoma and reversal of clinical drug resistance with chemotherapy plus high dose verapamil. J Clin Oncol 1991; 9: 17-24.
27. Goldstein LJ, Galski H, Fojo A, Willingham M, Lai SL, Gazdar A, Pirker R, Green A, Crist W, Brodeur GM. Expression of a multidrug resistance gene in human cancers. J Natl Cancer Inst 1989; 81: 116-124.
28. Filipits M, Jaeger U, Simonitsch I, Chizzali-Bonfadin C, Heinzl H, Pirker R. Clinical relevance of the lung resistance protein in diffuse large B cell lymphomas. Clin Cancer Res 2000; 6: 3417-3423.
29. Filipits M, Stranzl T, Pohl G, Heinzl H, Jäger U, Geissler K, Fonatsch C, Haas OA, Lechner K, Pirker R. Drug resistance factors in acute myeloid leukemia: a comperative analysis. Leukemia 2000; 14: 68-76.
30. den Boer ML, Pieters R, Kazemier KM, Rottier MM, Zwaan CM, Kaspers GJ, Janka-Schaub G, Henze G, Creutzig U, Scheper RJ, Veerman AJ. Relationship between major vault protein/lung resistance protein, multidrug resistance-associated protein, P-glycoprotein expression and drug resistance in childhood leukemia. Blood 1998; 91: 2092-2098.
31. Ohsawa M, Ikura Y, Fukushima H, Shirai N, Sugama Y, Suekane T, Hirayama M, Hino M, Ueda M. Immunohistochemical expression of multidrug resistance proteins as a predictor of poor response to chemotherapy and prognosis in patients with nodal diffuse large B cell lymphoma. Oncology 2005; 68: 422-431.
32. Huang WT, Huang CC, Weng SW, Eng HL. Expression of the multidrug resistance protein MRP and the lung resistance protein LRP in nasal NK/T cell lymphoma: further exploring the role of P53 and WT1 gene. Pathology 2009; 41: 127-132.
33. Li L, Su LP, Ma L, Zhao J, Zhu L, Zhou YA. Expression and significance of P-gp/mdr1 mRNA, MRP and LRP in non-Hodgkin's lymphoma. Zhonghua Zhong Liu Za Zhi 2009; 31: 199-202.
34. Zhan Z, Sandor VA, Gamelin E, Regis J, Dickstein B, Wilson W, Fojo AT, Bates SE. Expression of multidrug resistance associated protein gene in refractory lymphoma: quantitation by a validated polymerase chain reaction assay. Blood 1997; 89: 3795-3800.
35. Coiffier B. Monoclonal antibody as therapy for malignant lymphomas. C R Biol 2006; 329:241-254.
36. Ghetie MA, Marches R, Kufert S, Vitetta ES. An anti-CD19 antibody inhibits the interaction between P-gp and CD19, causes P-gp to translocate out of lipid rafts and chemosensitizes a MDR lymphoma cell line. Blood 2004; 104:178-183.
37. Klimecki WT, Futscher BW, Grogan TM, Dalton WS. P-glycoprotein expression and function in circulating blood cells from normal volunteers. Blood 1994; 83:2451-2458.