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Serum interleukin-10 levels are an independent prognostic factor for patients with Hodgkin's lymphoma

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Background and Objectives. Interleukin-10 (IL-10) is a pleiotropic cytokine which increases *bcl*-2 levels and protects cells from steroid or doxorubicin-induced apoptosis. Hodgkin and Reed-Sternberg (HRS) cells bear functional IL-10 receptors. Thus serum IL-10 (sIL-10) might inhibit apoptosis in HRS cells, which could occur as a result of either chemotherapy or the crippled immunoglobulin genes.

Design and Methods. We determined sIL-10 levels in 122 patients with Hodgkin's lymphoma (HL), treated with ABVD or equivalent regimens with or without radiotherapy, and correlated them with presenting clinical and laboratory features, as well as failure-free survival (FFS) and overall survival.

Results. Elevated sIL-10 levels (≥10pg/mL) were detected in 55 patients (45%), and were correlated with advanced stage and elevated serum β_2-microglobulin levels. At 7 years FFS was 85% vs. 63% for patients with normal vs. elevated sIL-10 levels, respectively (p=0.01); overall survival was 97% vs. 73% (p=0.005). Multivariate analysis with Cox's proportional hazards model demonstrated that elevated sIL-10 levels were the strongest independent predictor of FFS, and were also associated with inferior overall survival.

Interpretation and Conclusions. We conclude that sIL-10 levels are elevated in 45% of patients with HL, and are associated with inferior FFS and overall survival, independently of other established prognostic factors.

Key words: interleukin-10, serum levels, Hodgkin's lymphoma, prognostic factors, chemotherapy

Hodgkin's lymphoma (HL) is curable by chemotherapy (CT), combined modality therapy (chemotherapy plus radiotherapy; CMT) or radiotherapy (RT) alone. The ABVD regimen is considered as standard CT, either alone or in combination with MOPP in alternating or hybrid schedules, producing a high rate of durable complete remissions.[1-4] However, even after this treatment, 5-10% of early and 20-40% of advanced stage patients either progress during treatment or relapse following an initial remission.[4-13]

Pretreatment identification of patients with a high likelihood of failing to benefit from standard treatment is of paramount significance. Several investigators have attempted to identify such patients by formulating prognostic models based on clinical and routine laboratory parameters.[13-20] None of the described models, however, has been proven capable of selecting a sizeable group of patients with sufficiently low failure-free survival (FFS) to allow their inclusion in protocols using first-line intensified treatment. In addition, the clinical variables included in these models do not provide insight into the biology of HL or guidance for its rational treatment.

Recently, serum levels of various cytokines, cytokine receptors, or adhesion molecules have been correlated with disease activity and prognosis in HL.[21-31]

Interleukin-10 (IL-10) is a pleiotropic cytokine which is produced by activated T-cells and T_h-2 cell clones, activated monocytes and macrophages, stimulated B-cells and mast cells. IL-10 expression is detected within Hodgkin and Reed-Sternberg (HRS) cells, both at the protein[32] and mRNA level,[33] especially in HRS cells latently infected by Epstein-Barr virus (EBV).[32-34] In addition HRS cells bear functional IL-10 receptors.[35] IL-10 increases *bcl*-2 levels and protects B-cells, T-cells

and hematopoietic progenitors from apoptosis induced by glucocorticoids, doxorubicin or deprivation of growth factors.[36-40] Thus elevated serum IL-10 (sIL-10) levels might protect HRS cells from apoptotic stimuli arising either from their crippling mutations of the immunoglobulin locus[41] or from cytotoxic chemotherapy. At the clinical level, the MD Anderson group recently suggested that sIL-10 levels are elevated in approximately half of patients with HL and are strongly correlated with FFS independently of other factors.[34] However, other studies based on smaller patient series demonstrated a much lower frequency of elevated sIL-10 levels in HL.[23,42]

We, therefore, decided to determine sIL-10 levels in 122 patients with HL treated with ABVD or equivalent regimens with or without RT, in order to investigate their association with presenting clinical and laboratory features, FFS and overall survival.

Design and Methods

Patients

Patients with HL were selected for this study if they were older than 14 years, were HIV-negative, had pretreatment frozen serum available, and had received treatment with anthracycline-based chemotherapy with or without radiotherapy. Serum samples were collected between 1988 and 1999. During this period, 447 patients with HL received their primary treatment in the Hematology Section, Day Care Clinic of the Laikon General Hospital in Athens. Among them 424 had been treated with ABVD or equivalent regimens. Based on the selection criteria, 122 patients with HL formed the basis of the present study. Their characteristics were compared with those of 302 patients who had also received anthracycline-based chemotherapy with or without radiotherapy during the same period, but for whom pretreatment frozen serum samples were not available.

Staging and routine laboratory evaluations

All patients were clinically staged according to the Ann-Arbor system,[43] with history, complete physical examination, blood counts, biochemical profile, chest X-ray films, computed tomography of the chest, abdomen and pelvis, unilateral bone marrow biopsy, and bipedal lymphangiography. Hemoglobin concentration, white blood cell counts and differential, erythrocyte sedimentation rate (ESR), serum albumin and serum lactate dehydrogenase (LDH) levels were measured by standard assays. Anemia was defined as the presence of hemoglobin levels <13 g/dL for males and <11.5 g/dL for females. Serum albumin was analyzed at a cut-off of 3.5 g/dL, which was the lower normal limit in our laboratory. Serum β_2-microglobulin was measured by a radioimmunoassay (normal values: 1.0-2.4 mg/L).

Serum IL-10 level determination

IL-10 levels were determined in pretreatment serum samples, which had not been previously thawed and had been stored at –70°C, by a sandwich enzyme-linked immunoassay (human IL-10 Quantikine™; R&D Systems, Inc., Minneapolis, MN, USA), as previously described.[34] The assay was based on the use of an IL-10 specific monoclonal antibody, pre-coated onto a microplate. Any IL-10 present in standards and samples was bound by the immobilized antibody. After washing, a second IL-10 specific enzyme-linked polyclonal antibody was added to the wells. Following a wash, a substrate solution was added to the wells and color developed in proportion to the amount of IL-10 bound in the initial step. The color development was stopped and the intensity of the color was measured. Serum IL-10 levels were considered elevated if ≥10 pg/mL, based on analysis of levels in normal healthy volunteers, as previously described.[34] Furthermore we tested 21 additional serum samples from normal individuals. In this group, the mean value of sIL-10 levels was 5.3 pg/mL with a standard deviation of 2.6 pg/mL (range: 0-9.1 pg/mL). These values are comparable to those provided by the manufacturer.

Therapy

The treatment policy differed during the study period according to Ann Arbor clinical stage (AAS), as shown in Table 1. Early stage (IA, IIA) and most AAS IIIA patients received ABVD or EBVD plus low dose, involved field RT.[5] AAS IB, IIB, IIIB and IV patients were treated with alternating MOPP/ABVD,[2] the MOPP/ABV hybrid regimen[3] or ABVD, usually without RT (Table 1). All these regimens are currently considered equivalent.[4,10-12]

Statistical analysis

The distributions of the clinical and laboratory characteristics among patients with known and unknown sIL-10 levels and the frequency of elevated sIL-10 levels among various subgroups of patients defined by other known prognostic factors were compared by the chi-squared test.[44]

Failure-free survival (FFS) was defined as the time interval between treatment initiation and treatment failure or last follow-up. Failure was defined as inability to achieve complete or partial remission during initial therapy, requiring switch to another CT regimen, or progression after an initial complete or partial remission. Patients

Table 1. Treatment strategy applied in the 122 patients with Hodgkin's lymphoma under study.

Clinical stage	*Patients no.*	*Chemotherapy regimens no.*			*Radiotherapy no.*
		ABVD or EBVD	*MOPP/ABVD*	*MOPP/ABV*	
IA, IIA	73	73 (100)	-	-	71 (97)*
IB ,IIB	20	10 (50)	4 (20)	6 (30)	9 (45)°
IIIA	12	11 (92)	1 (8)	-	8 (67)*
IIIB, IV	17	7 (41)	6 (35)	4 (24)	2 (12)°
Total	122	101 (83)	11 (9)	10 (8)	90 (74)

*Numbers in brackets indicate percentages. *Low dose, involved field RT; °Low dose, involved field RT in 8 CS IIB and 1 CS IIIB patient; standard dose RT to the sites of residual disease in 1 CS IIB and 1 CS IVB patient.*

Table 2. Comparison of presenting clinical and laboratory features between patients with known and unknown sIL-10 levels.

Clinical or laboratory feature studied	sIL-10 levels: Known (n=122) #	%	Unknown (n=302) #	%	p
Age median (range)	31.5 (15-76)		30.0 (13-82)		0.65
≥45 years	27/122	22	63/302	21	0.77
Sex (male)	74/122	61	149/302	49	0.03
B-symptoms	37/122	31	106/302	35	0.35
Ann Arbor clinical stage					0.42
I	28/122	23	69/302	23	
II	65/122	53	144/302	48	
III	18/122	15	44/302	15	
IV	11/122	9	45/302	15	
Inguinal and/or iliac involvement	25/121	21	59/300	20	0.82
Histology					0.79
Nodular sclerosis	80/118	68	200/292	69	
Mixed cellularity	25/118	21	64/292	22	
Lymphocyte predominance	13/118	11	26/292	9	
Lymphocyte depletion	0	0	2/283	1	
Unclassified/unknown	4	–	10	–	
Anemia	37/121	31	108/290	37	0.20
White blood cells (≥15×10⁹/L)	14/119	12	50/291	17	0.17
Lymphocytopenia	11/105	11	26/239	11	0.91
ESR (≥30 mm 1st hour)	61/101	60	151/232	65	0.41
Serum albumin <3.5 g/dL	13/120	11	48/191	25	0.002
LDH levels elevated	20/82	24	66/200	33	0.11
β_2-microglobulin elevated	30/118	25	11/53	21	0.51

with toxic death during primary treatment or death in first remission, even if presumably attributed to long-term effects of treatment, were censored at the time of death. Overall survival was defined as the time interval between treatment initiation and death of any cause or last follow-up. The estimation of actuarial FFS or survival was performed by the method of Kaplan-Meier.[45] The identification of prognostic factors in univariate analysis was based on the log-rank test.[46] Independent prognostic factors were identified using Cox's proportional hazards model.[47] A forward stepwise selection procedure, with entry and removal criteria of p=0.05 and p=0.10, respectively, was used.

Results

Patient characteristics

The distribution of baseline clinical and laboratory characteristics was similar among the 122 patients with known and 302 patients with unknown serum IL-10 levels. In the patients with known sIL-10 levels, there was a higher percentage of males and lower percentage of patients with low serum albumin (Table 2).

Table 3. Correlation of sIL-10 levels with other known prognostic factors in 122 patients with Hodgkin's lymphoma.

Clinical or laboratory factors	sIL-10 ≥10pg/mL (%)	p§
Age (<45 vs ≥45 years)	43 vs 52	0.42
Sex (male vs female)	50 vs 38	0.17
B-symptoms (no vs yes)	40 vs 57	0.09
Ann Arbor clinical stage		
I vs II vs III vs IV	57 vs 32 vs 56 vs 73	0.02
I/IIA vs IIB/III/IV	41 vs 52	0.22
Inguinal/iliac involvement (no vs yes)	44 vs 48	0.70
Histology (NS vs MC vs LP)°	43 vs 48 vs 62	0.50
Anemia (no vs yes)	44 vs 47	0.94
White blood cells (< vs ≥15×10⁹/L)	45 vs 46	0.71
Lymphocytopenia (≥ vs <1.0×10⁹/L)	43 vs 73	0.06
ESR (< vs ≥30 mm the 1st hour)	38 vs 53	0.14
Serum albumin (≥3.5 vs < 3.5 g/dL)	44 vs 54	0.50
LDH levels (normal vs elevated)	37 vs 60	0.07
β_2-microglobulin (normal vs elevated)	39 vs 63	0.02

§Comparison of the frequencies of elevated sIL-10 levels by the chi-squared test; °NS=nodular sclerosis; MC=mixed cellularity; LP=lymphocyte predominance.

Serum IL-10 levels

The median value of pre-treatment sIL-10 was 8 pg/mL (range 0-109 pg/mL), and 55 of 122 patients (45%) had elevated (≥10 pg/mL) levels.

The correlation between sIL-10 levels and other known prognostic factors is shown in Table 3. sIL-10 levels were elevated in eight of 11 patients with AAS IV disease (73%), but in 16 of 28 (57%) patients with AAS I, 21 of 65 (32%) with AAS II, and 10 of 18 (56%) with AAS III disease (p=0.02). sIL-10 levels also correlated with elevated serum β_2-microglobulin levels (p=0.02). There was also a borderline correlation ($0.05<p<0.10$) between elevated sIL-10 levels and B-symptoms, lymphocytopenia, and elevated LDH levels.

Failure-free survival

Among the whole series of 424 patients, the median follow-up of currently alive patients was 42 months (6-136). It was 27 months (6-136) for patients with known sIL-10 levels, and 42 months (6-130) for those with unknown sIL-10 levels, reflecting the more recent policy of storing serum samples for IL-10 determination. The 7-year FFS was 75% for the 122 patients with known serum IL-10 levels and 80% for the 302 patients with unknown levels (p=0.27).

Elevated pre-treatment sIL-10 levels were strongly associated with treatment failure, since 7-year FFS was 85% vs 63% for patients with levels <10 and ≥10 pg/mL, respectively (p=0.01; Figure 1). Among patients

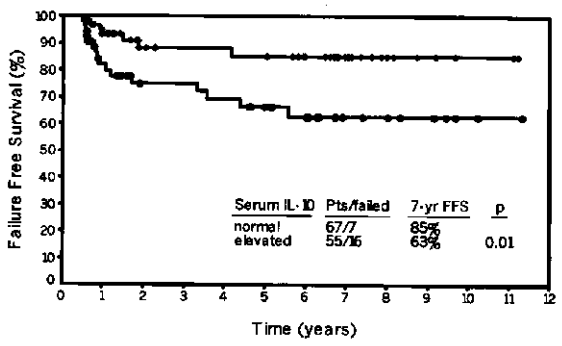

Figure 1. Effect of serum IL-10 levels on failure-free survival of 122 patients with Hodgkin's lymphoma, treated with ABVD or equivalent regimens, with or without radiation therapy.

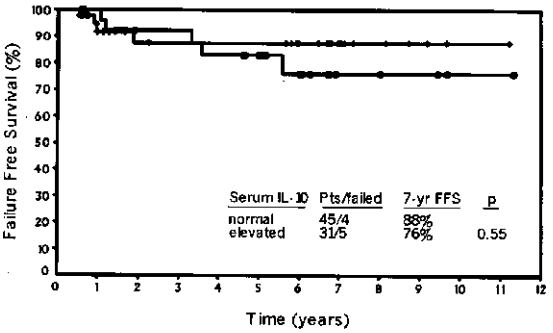

Figure 2. Effect of serum IL-10 levels on failure-free survival of 76 patients with Ann Arbor clinical stage I and IIA Hodgkin's lymphoma, treated with combined modality therapy based on ABVD or equivalent regimens.

Table 4. Univariate analysis of prognostic factors in 122 patients with Hodgkin's lymphoma.

Prognostic factor	*Patients (#)*	*7-year FFS (%)*	*p*
sIL-10 (< vs≥10 pg/mL)	67 vs 55	85 vs 63	0.01
Ann Arbor clinical stage (I/IIA vs IIB/III/IV)	76 vs 46	82 vs 62	0.0009
B-symptoms (no vs yes)	85 vs 37	81 vs 61	0.02
Inguinal and/or iliac involvement (no vs yes)	96 vs 25	80 vs 47	0.005
Age (<45 vs ≥45 years)	95 vs 27	76 vs 70	0.80
Sex (male vs female)	74 vs 48	73 vs 77	0.80
Histology (NS vs MC vs LP)°	80 vs 25 vs 13	79 vs 65 vs 57	0.64
Anemia (no vs yes)	84 vs 37	77 vs 69	0.26
White blood cells (< vs ≥15×10⁹/L)	105 vs 14	74 vs 75	0.59
Lymphocytopenia (≥vs<1.0×10⁹/L)	94 vs 11	75 vs 38	0.01
ESR (< vs ≥30 the 1st hour)	40 vs 61	74 vs 68	0.22
Serum albumin (≥ vs < 3.5 g/dL)	107 vs 13	76 vs 63	0.35
LDH levels (normal vs elevated)	62 vs 20	83 vs 63	0.05
β_2-microglobulin (normal vs elevated)	88 vs 30	78 vs 61	0.04

°NS=nodular sclerosis; MC=mixed cellularity; LP=lymphocyte predominance.

with early stage disease (AAS IA and IIA), the 7-year FFS for those with serum IL-10 levels <10 and ≥10 pg/mL was 88% and 76%, respectively (p=0.55), as shown in Figure 2. The corresponding figures among patients with advanced stage disease (IIB, III, IV) were 80% and 44%, respectively (p=0.009; Figure 3).

The results of univariate FFS analysis are shown in Table 4. Except for pre-treatment sIL-10 levels, significant predictors of FFS were: AAS (I/IIA vs IIB/III/IV, p=0.0009), B-symptoms (p=0.02), inguinal and/or iliac involvement (p=0.005), lymphocytopenia (p=0.01), elevated LDH (p=0.05) and β_2-microglobulin levels (p=0.04). These factors have been previously described by others.[7,13-17,22]

When sIL-10 levels, AAS (I/IIA vs IIB/III/IV), B-symptoms, β_2-microglobulin and inguinal/iliac involvement were examined in a multivariate model of FFS, B-symptoms and β_2-microglobulin were rejected. Pre-treatment sIL-10 levels became the more potent predictor of FFS (p=0.008), followed by clinical stage (p=0.03) and inguinal and/or iliac involvement (p=0.04). The results of multivariate analysis are shown in Table 5. Lymphocytopenia, ESR or LDH levels were not entered as covariates, because this information was missing for many patients.

Overall survival

The 7-year overall survival was 84% vs 89% for patients with known and unknown serum IL-10 levels, respectively (p=0.27).

Elevated pre-treatment serum IL-10 levels were also predictive of overall survival (p=0.005; Figure 4). Other significant predictors of overall survival in univariate analysis were Ann Arbor clinical stage (IIB/III/IV vs I/IIA, p=0.005), inguinal/iliac involvement (p=0.0002), anemia (p=0.01), lymphocytopenia (p=0.0003), ESR ≥50 (p=0.04), hypoalbuminemia (p=0.02), elevated LDH (p=0.0005) and β_2-microglobulin (p=0.0001). In multivariate analysis, independent predictors of overall survival were elevated sIL-10 levels (p=0.005), anemia (p=0.005), inguinal/iliac involvement (p=0.003), and elevated β_2-microglobulin (p=0.02).

Discussion

In the present study we confirm that sIL-10 levels are frequently elevated in HL and that they are associated with inferior FFS and overall survival in patients treated with ABVD or equivalent regimens, independently of AAS and other known adverse prognostic factors.

Values of sIL-10 ≥10 pg/mL, which are higher than those seen in normal volunteers, as shown by our data as well as those presented in ref. #34, were considered elevated. Using this cut-off value, 45% of our patients had elevated sIL-10 levels, in agreement with the frequency of 45-50% reported in other series.[34,48] In the MD Anderson series, however, in which 50% of the patients had elevated sIL-10 levels, a clearly higher proportion of patients had AAS III/IV, which was shown to be associated with higher sIL-10 levels. The findings of

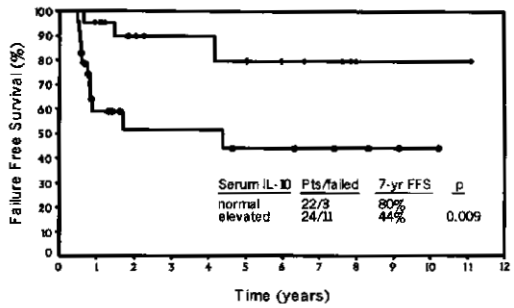

Figure 3. Effect of serum IL-10 levels on failure-free survival of 46 patients with Ann Arbor clinical stage IIB, III and IV Hodgkin's lymphoma, treated with ABVD or equivalent regimens, with or without radiation therapy.

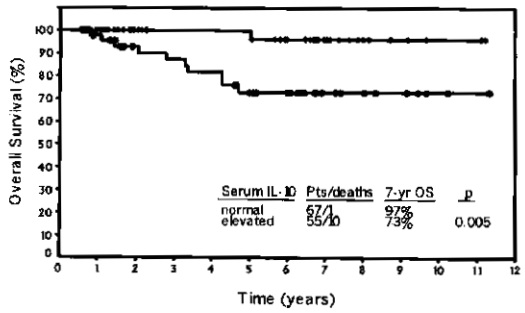

Figure 4. Effect of serum IL-10 levels on overall survival of 122 patients with Hodgkin's lymphoma, treated with ABVD or equivalent regimens, with or without radiation therapy.

both studies are in marked contrast with recently published, smaller series of 31 and 64 HL patients, in which only 3% and 14% had elevated sIL-10 levels.[23,42] This discrepancy may be due to different patient populations seen at various centers and underscores the difficulty in comparing treatment results between centers.

Using the chi-squared test, we compared the frequency of elevated sIL-10 levels in various groups of patients defined by other known prognostic factors. We found that sIL-10 levels were higher in patients with advanced AAS, especially IV, and elevated β_2-microglobulin levels. In agreement with previously reported results, there was a marginally significant correlation between high sIL-10 levels and B-symptoms and abnormal LDH, as well as with lymphocytopenia. However the strong relationship between high sIL-10 levels and older age, mixed cellularity histology, hypoalbuminemia or anemia,[34] was not confirmed in this study.

In multivariate analysis, the presence of elevated pretreatment sIL-10 levels was the strongest prognostic factor for FFS (p=0.008), followed by clinical stage IIB/III/IV (p=0.03) and inguinal/iliac involvement (p=0.04). The prognostic impact of sIL-10 was impressive among advanced stage patients (IIB, III, IV; Figure 3). Furthermore, sIL-10 levels were also predictive of overall survival independently of AAS.

Table 5. Multivariate analysis of prognostic factors for failure-free survival in 122 patients with Hodgkin's lymphoma.

Prognostic factor	Relative risk of failure RR	95% CI	p
sIL-10 (≥10 vs <10 pg/mL)	3.4	1.4-8.3	0.008
Ann Arbor clinical stage (IIB/III/IV vs I/IIA)	2.7	1.1-6.4	0.03
Inguinal and/or iliac involvement (yes vs no)	2.5	1.1-6.1	0.04

Abbreviations: RR=relative risk; 95% CI= 95% confidence intervals.

When considered as a prognostic factor, sIL-10 has the significant advantage of being elevated in a substantial proportion (up to 50%) of patients. This is in contrast with most other established prognostic factors, in which the size of the adverse prognostic group rarely exceeds 25% of the patient population. Thus sIL-10 may significantly contribute to the identification of sizeable subgroups of patients with sufficiently low FFS to justify an aggressive first-line treatment approach. Furthermore, most conventional prognostic factors are probably secondary variables caused by complex, poorly understood host-tumor interactions. In contrast, sIL-10 levels may represent a *primary* variable, which may be involved in the biological processes of HL.

We did not examine the relationship of sIL-10 levels and the value of the International Prognostic Score (IPS) described by Hasenclever and Diehl,[13] because IPS was developed for advanced stage patients, who represented a minority in our patient population. IPS works, but is less potent, in predicting the outcome of early stage patients, most of whom have scores <3.[49] According to our results sIL-10 was more discriminative in advanced stage HL than in early stages. Furthermore, among the 7 factors evaluated in the IPS, sIL-10 levels were only correlated with stage IV. Thus, we hope that sIL-10 levels may represent a prognostic factor, independent of the IPS value. This issue should be explored in larger patient populations. Furthermore sIL-10 might improve the ability of IPS to define a sizeable subgroup of patients with HL and FFS <40-50%, in order that they may be considered for *experimental* first-line treatment, such as high-dose therapy with stem cell support.

At the biological level, within the neoplastic HL tissue, IL-10 is produced by the HRS cells and, to a lesser degree, by reactive lymphocytes,[32] being exclusively of cellular and not viral origin.[32] The expression of IL-10 mRNA is much more prominent in EBV-associated cases[33] and may explain the immunologic escape of LMP-1 expressing HRS cells. However, even EBV-negative cases may express a certain level of IL-10,[32] and may have elevated sIL-10 levels. Since HRS cells bear func-

tional IL-10 receptors,[35] elevated sIL-10 levels might upregulate *bcl*-2 expression in these cells in an autocrine fashion, thus preventing apoptosis. Recently there has been evidence that *bcl*-2 is detectable in approximately 60% of HL cases and that *bcl*-2 positivity may be a strong adverse prognostic factor for FFS.[50,51] Whether the prognostic impact of *bcl*-2 expression is independent of sIL-10 levels must be further investigated. However the exact role of IL-10 in the pathogenetic mechanisms of proliferation and apoptosis of HRS cells has not yet been firmly established.

In the present study we confirmed the previous report suggesting that elevated sIL-10 is associated with inferior FFS in patients with HL[34] treated with ABVD or equivalent regimens in an independent and larger group of patients from a single center. Other groups have demonstrated an adverse impact of elevated sIL-10 on FFS, but the numbers of patients were small,[42,48] frequently including a considerable percentage of radiotherapy-treated patients, who are known to have an inferior FFS.[42,52] Multivariate analysis results have been reported only by Viviani *et al.* and demonstrated the independent prognostic significance of sIL-10 levels in 73 patients.[48]

In conclusion, multivariate analysis demonstrated that sIL-10 is an independent predictor of FFS in our patients, although there are limitations due to the relatively low number of failures. Larger numbers of patients are required to build sIL-10-based models for the identification of patients with HL who are at a particularly high risk of treatment failure. Such efforts should also co-examine all potentially relevant clinical and routine laboratory variables, as well as other biological factors, including EBV and *bcl-2* expression and possibly serum levels of various other molecules.

Contributions and Acknowledgments

TPV was primarily responsible for this work from conception to submitted manuscript, and should be considered as the principal author. All authors qualified for authorship according to the World Association of Medical Editors (WAME) criteria, and have taken specific responsibilities, as described below: TPV, AHS: statistical analysis; GN: laboratory experiments; TPV, MKA: collection of data; GAP, TPV, MKA, MPS, MND, FNK, MH, GV: management of clinical data covering a long follow-up period; GZR, IADA, CK: pathology review; GAP, AHS, GP: study supervisors, responsibility from conception to submitted manuscript, and final approval of the manuscript. All authors contributed to the writing of the paper. The authors are listed according to a criterion of decreasing individual contribution to the work, with the following exceptions: the last author had a major role as senior author in designing the study, interpreting the data, and preparing the article, while AHS and GP were study supervisors, and took responsibility for this work from conception to submitted manuscript.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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Potential implications for clinical practice

- More than half of patients with advanced Hodgkin's lymphoma have elevated sIL-10 levels and probably have a poor prognosis, with a FFS of 40-45%.
- This study forms a solid background in order to explore the prognostic impact of sIL-10 further in larger series of patients with Hodgkin's lymphoma and strengthens the rationale of building prognostic models incorporating biological factors.

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