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ORIGINAL ARTICLE

Limited usefulness of CA125 measurement in the management of Hodgkin's and non-Hodgkin's lymphoma

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Abstract

Background: Several papers have reported an association of high CA125 serum levels with advanced non-Hodgkin's lymphoma (NHL) as well as a relationship between high CA125 values and poor outcome. *Patients and methods:* Ninety-nine patients with NHL or Hodgkin's disease (HD) underwent serum CA125 assessment at diagnosis. Gender, age, presence of B symptoms, performance status (PS), histology, sites of tumor involvement, presence of effusion, clinical stage, age-adjusted International Prognostic Index, C-reactive protein (CRP), Hb, lactate deshydrogenase (LDH) and β2-microglobulin were evaluated for their association with serum CA125 levels. The impact of CA125 levels and other features on overall (OS) and progression-free (PFS) survival was also assessed. *Results:* CA125 serum levels were elevated in 34% of the patients, including 19% of patients with aggressive NHL, 45% of patients with indolent NHL, and 29% of patients with HD. Univariate analyses showed that CA125 levels correlated with poor PS, the presence of B symptoms, advanced clinical stage, abdominal, bone marrow or mediastinal involvement, presence of effusions, high aaIPI, low Hb levels and high CRP, LDH or β2-microglobulin levels. In multivariate analysis, bone marrow involvement, the presence of effusions, and high aaIPI were all associated with high CA125 serum levels. In univariate analyses, OS and PFS were affected by age (PFS only), poor PS, B symptoms, advanced clinical stage, bone marrow or abdominal involvement (PFS only), high aaIPI, low Hb, high CRP or β2-microglobulin levels. OS and PFS were not different in patients with normal or elevated CA125 levels. Multivariate analyses showed significantly inferior OS and PFS in patients with high β2-microglobulin but no influence of CA125. *Conclusion:* While CA125 serum level correlates significantly with a number of features associated with more aggressive disease, it does not enhance the performance of standard prognostic markers in the management of patients with NHL or HD.

Key words CA125; non-Hodgkin's lymphoma; Hodgkin's disease

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CA125 is a glycoprotein (200 KD) expressed by epithelial ovarian tumors. CA125 levels in serum can be used to follow response to treatment in patients with ovarian carcinoma. However, elevated CA125 serum levels have also been reported in other gynecological pathologies, some non-gynecological malignant disorders and even in benign pleural or abdominal effusions (1, 2).

Since 1995, several papers reported the association of high CA125 serum levels with non-Hodgkin's lymphoma (NHL). With the exception of age, most of the IPI's (3) factors were found to be associated with high CA125 levels in six prospective or retrospective studies (1, 2, 4–7). Bulky disease and/or high tumor burden were reported to be associated with high CA125 levels in seven studies (1, 2, 4,

5, 7–9). Produced by mesothelial cells, this biological marker appeared to be strongly correlated with the presence of effusions and abdominal involvement. The association with B symptoms or bone marrow involvement has also been described in some studies (1, 4, 6, 7, 9, 10). Finally, CA125 serum level at diagnosis has been reported to be a new prognostic factor (1, 4, 6, 7) and it has been proposed to incorporate it in the current prognostic index. On the other hand, CA125 levels have rarely been examined in patients with Hodgkin's disease (HD).

In this study, we analyzed the clinical characteristics associated with elevated CA125 levels at diagnosis and examined whether abnormal CA125 serum levels were associated with altered overall survival (OS) or progressive-free survival (PFS) in 99 patients with HD or NHL.

Patients and methods

Patients

Between July 2000 and January 2005, 99 consecutive patients hospitalized in our center with newly diagnosed NHL or HD underwent serum CA125 assessment at diagnosis. Their characteristics are detailed in Table 1. Tumors were classified according to the REAL classification (11). The extent of the disease was evaluated by means of physical examination, computed tomography of the chest, abdomen and pelvis, total body PET scanner, bone marrow biopsy, as well as other investigations depending on clinical symptoms and signs. Staging was defined on the basis of the Ann Arbor classification (12). Performance status was assessed according to the Eastern Cooperative Oncology Group scale.

Laboratory analyses

All laboratory analyses were determined on fresh samples collected on the same day at diagnosis. Serum CA125 was measured on a Modular E170 autoanalyser by Electrochemiluminescence Immunoassay (Roche, Basel, Switzerland) with a measuring range of 0.6–5000 UI/mL (reference range 0–35 UI/mL). Serum β_2-microglobulin (Radioimmunoassay; Immunotech, Prague, Czech Republic, reference range 1–2.5 mg/L), serum lactate deshydrogenase (LDH) (enzymatic UV-assay; Roche, reference range 240–480 UI/L), hemoglobin (Cyanmethemoglobin method; Bayer Technicon, Tarrytown, NY, USA) and C-reactive protein (CRP) (Immunoturbidimetric assay; Roche) were also obtained in all patients.

Statistical analyses

Results were expressed as means ± standard deviations, medians and ranges for continuous variables and as percentages for categorical variables. Biological parameters were log-transformed whenever appropriate. Patients with normal or elevated CA125 levels were compared by logistic regression for each variable separately but also for all variables combined into a backward selection procedure (13). OS and PFS were evaluated by Cox regression models with application of a backward selection procedure. Multivariate analyses were carried out by adjusting for the histological group and in the case of OS and PFS for CA125 levels. Results were considered to be significant at the 5% level ($P < 0.05$). Data analysis was carried out using SAS 9.1 for Windows (SAS Institute, Cary, NC, USA) statistical package.

Results

Characteristics of the patients (demography, clinical and biological parameters) are listed in Table 1 for the total population and within each histological group. There were 27 patients with indolent NHL (Lymphocytic lymphoma $n = 1$, follicular lymphoma $n = 15$, malt lymphoma $n = 6$, unclassified $n = 5$), 51 with aggressive NHL (Diffuse large B cell lymphoma $n = 39$, mantle cell lymphoma $n = 6$, anaplastic large cell lymphoma $n = 2$, periperal T-cell lymphoma $n = 3$, Burkitt's lymphoma $n = 1$) and 21 patients with HD (Nodular lymphocyte-predominant HD $n = 3$, nodular sclerosis HD $n = 16$, mixed cellularity HD $n = 1$, unclassified HD $n = 1$). There were 42 (42%) women and 57 (58%) men, mean age was 57 ± 18 yr (median 58 yr, range 15–88 yr). Among patients, 17% had poor performance status, 22% presented B symptoms, 58% had an advanced clinical stage, 50% abdominal, 40% mediastinal and 28% bone marrow involvement, and 14% an effusion. The aaIPI was ≥1 in 37% of the patients.

CA125 serum level was 105 ± 368 UI/mL and was elevated in 34 patients (34%). Proportions of patients with elevated CA125 serum levels did not significantly differ among the three histological groups (indolent NHL: 19%, aggressive NHL: 45%, HD: 29%; $P = 0.059$). There was also no significant difference for age ($P = 0.46$) and sex ($P = 0.86$). Patients with elevated CA125 serum levels had more frequently poor performance status (37% vs. 8%, $P = 0.0015$), B symptoms (42% vs. 11%, $P = 0.0009$), advanced clinical stage (88% vs. 42%, $P < 0.0001$), abdominal (74% vs. 37%, $P = 0.0008$), mediastinal (62% vs. 29%, $P = 0.002$) or bone marrow (47% vs. 19%, $P = 0.004$) involvement and presence of effusions (36% vs. 2%, $P = 0.0009$). They had also higher aaIPI (75% vs. 17%, $P < 0.0001$). Finally, they exhibited lower Hb levels (12 ± 2.4 vs. 14 ± 1.9 g/dL, $P = 0.002$), higher CRP (58 ± 83 vs. 21 ± 33 mg/L, $P = 0.0003$), LDH (900 ± 883 vs. 500 ± 530 UI/L, $P < 0.0001$) and β2-microglobulin (4.1 ± 2.7 vs. 2.2 ± 1.3 mg/L, $P < 0.0001$) levels.

Table 1 Patient's characteristics* according to histology and for the total population

Variable	Non-Hodgkin's lymphoma		Hodgkin's disease ($n = 21$)	Total population ($n = 99$)
	Indolent lymphoma ($n = 27$)	Aggressive lymphoma ($n = 51$)		
Demography				
Age (years)	59 ± 13 (58, 36–80)	64 ± 14 (65, 26–88)	37 ± 18 (32, 15–78)	57 ± 18 (58, 15–88)
Sex				
Female	44	35	57	42
Male	56	65	43	58
Clinical parameters				
Performance status				
0–1	92	77	85	82
≥2	8	23	15	17
B symptoms				
No	85	80	67	78
Yes	15	20	33	22
Ann Arbor stage				
I	37	16	14	21
II	3.7	16	57	21
III	3.7	18	9.5	12
IV	56	51	19	46
Sites of tumor				
Abdominal	63	53	24	50
Mediastinal	22	33	81	40
Bone Marrow	44	26	14	28
Effusion	13	16	9.5	14
aaIPI				
0	35	21	48	31
1	46	27	29	33
2	15	31	24	25
3	3.9	21	0	12
Biological parameters				
CA125 (UI/mL)	77 ± 269 (17, 7–1418)	147 ± 471 (30, 4–3050)	39 ± 44 (20, 9–144)	105 ± 368 (21, 4–3050)
% elevated (≥35 UI/mL)	19	45	29	34
Hb (g/dL)	14.0 ± 2.0 (14.4, 8.9–18.0)	13.1 ± 2.2 (13.4, 7.8–16.9)	12.6 ± 2.3 (12.8, 8.5–15.8)	13.2 ± 2.2 (13.5, 7.8–18.0)
CRP (mg/L)	11 ± 15 (3, 2–56)	41 ± 68 (15, 1–390)	45 ± 59 (27, 2–240)	34 ± 58 (13, 1–390)
LDH (UI/L)	388 ± 135 (358, 185–797)	841 ± 912 (561, 296–5028)	463 ± 199 (392, 272–1119)	635 ± 692 (431, 185–5028)
β2–microglobulin (mg/L)	2.7 ± 1.8 (2.0, 1.3–8.9)	3.3 ± 2.4 (2.3, 1.0–12.0)	2.2 ± 1.2 (1.8, 0.9–5.7)	2.9 ± 2.1 (2.0, 0.9–12.0)

Hb, hemoglobin; CRP, C-reactive protein; LDH, lactate deshydrogenase.

* For continuous variables: mean ± SD (median, range) and for categorical variables: %.

When the analysis was restricted to patients with indolent lymphomas, those with elevated CA125 serum levels had more often mediastinal involvement (60% vs. 14%, $P = 0.042$), higher aaIPI (60% vs. 10%, $P = 0.024$), higher LDH (564 ± 186 vs. 348 ± 82 UI/L, $P = 0.022$), CRP (25 ± 23 vs. 7 ± 10 mg/L, $P = 0.049$) and β2-microglobulin (5.0 ± 2.8 vs. 2.1 ± 0.8 mg/L, $P = 0.024$) levels.

In aggressive NHL, patients with elevated CA125 serum levels had more frequently poor performance status (40% vs. 11%, $P = 0.028$), B symptoms (41% vs. 4%, $P = 0.0091$), advanced clinical stage (96% vs. 46%, $P = 0.003$), abdominal (78% vs. 32%, $P = 0.0017$), mediastinal (52% vs. 18%, $P = 0.013$) or bone marrow (44% vs. 11%, $P = 0.012$) involvement, high aaIPI (81% vs. 30%, $P = 0.0009$), low Hb (12 ± 2.5 vs. 14 ± 1.7 g/dL, $P = 0.027$), high CRP (63 ± 91 vs. 24 ± 34 mg/L, $P = 0.043$), LDH (1051 ± 1045 vs. 677 ± 778 UI/L, $P = 0.0081$) or β2-microglobulin (4.3 ± 2.9 vs. 2.5 ± 1.7 mg/L, $P = 0.0057$) levels.

Table 2 Univariate Cox analyses for progression-free and overall survival

	Overall survival		Progression-free survival	
Variable	Hazard ratio	*P*-value	Hazard ratio	*P*-value
Histology				
Lymphoma[1]				
Indolent	0.71	0.67	2.5	0.16
Aggressive	2.26	0.20	2.7	0.11
Demography				
Age (years)	1.02	0.08	1.03	0.004
Sex				
Male	1.09	0.85	1.6	0.19
Clinical parameters				
Performance status				
2–3	5.1	0.0005	3.0	0.007
B symptoms				
Yes	4.3	0.0014	2.3	0.031
Ann Arbor stage				
III–IV	3.3	0.033	4.6	0.0019
Sites of tumor				
Abdominal	1.7	0.23	2.8	0.0088
Mediastinal	2.3	0.06	1.1	0.71
Bone marrow	2.8	0.02	2.9	0.003
Effusion	1.2	0.81	1.9	0.18
AaIPI				
2–3	5.3	0.0006	3.9	0.0004
Biological parameters				
CA125				
≥ 35 UI/mL	1.8	0.20	1.8	0.11
Hb (g/dL)[2]	0.03	0.001	0.15	0.035
CRP (mg/L)[2]	1.5	0.007	1.3	0.036
LDH (UI/L) [2]	1.8	0.06	1.6	0.057
β2–microglobulin (mg/L) [2]	5.9	<0.0001	4.1	<0.0001

Hb, hemoglobin; CRP, C-reactive protein; LDH, lactate deshydrogenase.
[1] Reference = Hodgkin's disease.
[2] Log-transformation.

In multivariate analysis adjusted for histological group, only bone marrow involvement ($P = 0.032$), the presence of effusion ($P = 0.009$) and high aaIPI ($P = 0.002$) were significantly associated with high CA125 serum levels.

OS was significantly worse for patients with poor performance status hazard ratio (HR = 5.1, $P < 0.0005$), B symptoms (HR = 4.3, $P = 0.0014$), advanced clinical stage (HR = 3.3, $P = 0.033$), bone marrow involvement (HR = 2.8, $P = 0.02$), high aaIPI (HR = 5.3, $P = 0.0006$), low Hb (HR = 0.03, $P = 0.001$), high CRP (HR = 1.5, $P = 0.007$) and high β2-microglobulin (HR = 5.9, $P < 0.0001$) (Table 2, Fig. 1). Progression-free survival (PFS) was significantly worse for older patients (HR = 1.03, $P = 0.004$), those with poor performance status (HR = 3.0, $P = 0.007$), B symptoms (HR = 2.3, $P = 0.031$), advanced clinical stage (HR = 4.6, $P = 0.0019$), abdominal (HR = 2.8, $P = 0.009$) as well as bone marrow (HR = 2.9, $P = 0.003$) involvement, high aaIPI (HR = 3.9, $P = 0.0004$), low Hb (HR = 0.15, $P = 0.035$), high CRP (HR = 1.3, $P = 0.036$) and high β2-microglobulin (HR = 4.1, $P < 0.0001$) (Table 2). OS and PFS were not different in patients with normal or elevated CA125 levels.

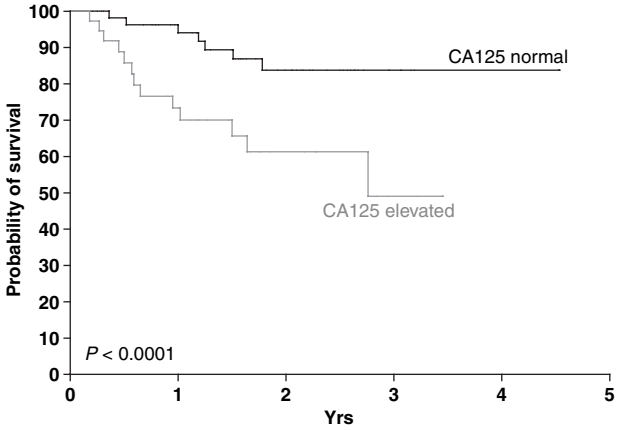

Figure 1 Overall Survival according to β2-microglobulin level at diagnosis.

In multivariate Cox models, when adjusting for CA125 levels and for histological group, OS and PFS were significantly affected adversely only by high β2-microglobulin (OS: HR = 7.1, $P < 0.0001$; PFS: HR = 5.9, $P < 0.0001$) (Table 3). For PFS, we also noted a worse outcome for men (HR = 2.7, $P = 0.015$). There was no effect of CA125 levels (OS, $P = 0.18$; PFS, $P = 0.48$) and no difference between histological groups (OS: $P > 0.5$; PFS: $P > 0.5$).

Discussion

In this study, we retrospectively evaluated the significance of CA125 serum levels in 99 patients with lymphoma. We first analyzed the clinical and biological characteristics associated with elevated CA125 levels at diagnosis. High CA125 serum levels were observed in 34% of the patients. This percentage is comparable with figures previously reported by other authors (2, 5–7, 14–17). In univariate analysis, many characteristics of more advanced disease were associated with elevated CA125 values. However, in multivariate analysis, an association was only found between high CA125 serum levels, on the one hand, and the presence of effusions, marrow involvement and high aaIPI, on the other. These results have been previously found by others (1, 2, 4–10, 17).

It is now proven that it is not the malignant lymphocytes but mesothelial cells that produce CA125 (1, 4, 5, 10, 14). Inflammatory cytokines, such as IL-1 and TNF-α, produced by macrophages and lymphoma cells, are

Table 3 Multivariate Cox analyses (adjusted for histology and CA125 level) for progression-free and overall survival

Variable	Overall survival			Progression-free survival		
	P-value	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI
Lymphoma[1]						
Indolent	0.8336	0.82	0.13–5.00	0.0972	3.74	0.79–17.76
Aggressive	0.3871	1.95	0.43–8.89	0.1417	3.12	0.68–14.23
CA125 (UI/L)	0.1795	0.48	0.16–1.40	0.4772	0.70	0.27–1.86
β2–microglobulin (mg/L)	<0.0001	7.13	2.82–18.01	<0.0001	5.93	2.58–13.60
Male sex	-	-	-	0.0146	2.72	1.22–6.06

[1] Reference = Hodgkin's disease.

suspected to stimulate CA125 (1, 4, 14), but also IL-6 and IL-8 production (5, 15). The presence of effusion or the involvement of serous membranes (such as the peritoneum, pericardium or pleura) can thus enhance CA125 production by mesothelial cells (1, 2). Because of CA125 production by cells other than lymphoma cells, its serum levels are more a reflection of the inflammatory response to the disease than of the tumor mass itself. As cytokine production is proportional to the tumor mass (15), it is not surprising that CA125 are mostly found in association with various characteristics of advanced disease.

We now have good prognostic factors, such as the aaIPI (3) for aggressive NHL and the FLIPI (18) for follicular lymphoma. Given the association of CA125 levels with higher aaIPI, the gold standard of prognostic evaluation of lymphoma patients, one could predict that CA125 levels would not enhance that prognostic assessment. Indeed, CA125 serum levels did not improve its performance in our study. It would therefore be inappropriate to take therapeutic decisions based on CA125 serum levels.

Some authors have reported worse outcome in patients with high CA125 levels (1, 4, 7, 8). In univariate analysis, Bairey *et al.* (4) found significantly worse OS in patients with aggressive NHL and elevated CA125 but this biological factor lost its prognostic significance in multivariate analysis. Zacharos *et al.* (1) observed 5-yr survival of 65% vs. 20% in patients with aggressive NHL and normal or elevated CA125, respectively. This difference remained significant in multivariate analysis. Benboubker *et al.* (7) reported significantly better outcome in patients with low-grade NHL and normal CA125 levels but the results of multivariate analyses are unknown. Finally, in a study of 38 patients, Zidan *et al.* (6) showed inferior OS for patients with aggressive NHL and high CA125 levels (5-yr OS: 35% vs. 76%, respectively). This difference remained significant after the population was split into histological subgroups. We were not able to confirm this. In our series, only β2-microglobulin worsened PFS or OS. This result has already been reported and is now well validated (15). These contradictory results could be related to different patient populations and treatments, and should be better investigated in multicenter studies including more patients, receiving the same treatment and presenting homogenous histological and clinical features.

The role of CA125 levels in the early detection of relapse in CA125-producing patients has also been reported (1, 2, 4, 6). Perhaps, other methods, such as PET scans or combined CT-PET scans (19), would be more efficient, though more costly but this remains to be prove. However, the decrease of CA125 serum levels during therapy could be an argument for adequate tumor response to therapy in so far as there are no concomitant abdominal, pericardial or pleural abnormalities.

In conclusion, while CA125 serum level correlates with a number of features associated with more aggressive disease, it does not enhance the performance of standard prognostic factors in the treatment of patients with NHL or HD.

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