The prognostic value of Serum CD163, TARC, and β2 Microglobulin as response biomarkers in Hodgkin's lymphoma

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Abstract: Background: Precise diagnosis and prediction of the prognosis is crucial for determining the optimal treatment strategy for Hodgkin's lymphoma (HL). This study aimed to investigate the prognostic utility of serum TARC, CD163 and Serum β2MG in HL. **Methods:** a multicenter prospective observational study was conducted on 84 patients with HL. Serum TARC and CD163 were quantified using ELISA techniques, while β2MG was assessed using radioimmunoassay. **Results:** Among the included patients, 32 were with advanced stages and 23 were treated with ABVD only. There were significant differences between either early and advanced stages or partial and complete disease response regarding the baseline of these three biomarkers ($P<0.05$). The ROC analysis showed that TARC, CD163, and β2MG had high diagnostic values in highlighting the advanced stages (AUC=0.84; $P<0.001$, AUC=0.79; $P<0.001$, and AUC=0.78; $P<0.001$, respectively). TARC showed the highest specificity, while β2MG showed the highest sensitivity. The Kaplan-Meier analysis showed that β2MG, CD163, and TARC were associated with good prognostic function and disease response prediction. **Conclusion:** Serum TARC and CD163 are good prognostic biomarkers for follow up of HL. Serial TARC, CD163, or β2MG measurements accurately reflected disease activity and response. Furthermore, the levels of TARC, CD163, and β2MG were reported to be highly associated with the disease severity.

[Hossam Darwish, Mohamed A. Alm El-Din, Lamiaa A. Barakat, Rania M. Bondok and Sheren Waly. **The prognostic value of Serum CD163, TARC, and β2Microglobulin as response biomarkers in Hodgkin's lymphoma.** *Cancer Biology* 2019;9(2):1-8]. ISSN: 2150-1041 (print); ISSN: 2150-105X (online). http://www.cancerbio.net. 1. doi:10.7537/marscbj090219.01.

Keywords: TARC, CD163, β2MG, Hodgkin's lymphoma.

1. Introduction

Hodgkin's Lymphoma (HL) is a chronic, progressive, neoplastic disorder associated with uncontrolled inflammatory response of the lymphatic tissue. Primarily, it affects lymph nodes, but it may progress to extra lymphatic sites as liver, spleen and bone marrow(1). Importantly, HL is one of the most curable malignancies with high survival rates(2). According to the Surveillance, Epidemiology, and End Results (SEER) Program, the 5-year survival rate has been on a continuous rise during the past ten years, reaching more than 90% in early stages and more than 80% in the advanced stages(3, 4). Nevertheless, a minority of cases does not optimally respond to the first line chemotherapeutic agents, exposing them to the unnecessary long-term toxicity(5). Consequently, the main focus of the current clinical research is to early define the refractory cases through more applicable prognostic tools. It has been reported that combined Computed Tomography with Positron Emission Tomography (CT/PET) scan is the currently used tool to determine chemosensitivity and assess treatment efficacy(6, 7). However, CT/PET is not the ideal tool. It has a poor positive predictive value, costly, and not easily applicable to do in each follow-up visit. In addition, it lacks accuracy, as interpretation may be influenced by a synchronous inflammation or infection(8). Moreover, detection of tissue biomarkers carries prognostic information but it is not the ideal tool for monitoring disease response and treatment efficacy(9). Blood-based biomarkers may carry hope, being much more practical, highly tolerable and economic. Nevertheless, blood-based biomarkers must have high specificity and sensitivity, at least comparable to the currently-used imaging method. The serum level of beta-2 microglobulin (β2MG), a protein that present on the surface of nearly all nucleated cells, was reported to be useful in the prognosis of several lymphoid malignancies (10-12). It was reported to have favorable prognostic value in HL, especially in the advanced classic HL (13-15), thus it is used routinely as a biomarker for HL in our clinical practice. However, there is a controversy regarding its independence in the prognosis and monitoring the disease response(15).

Having the classic HL, the non-neoplastic tumor-infiltrating microenvironment accounts for the majority of the tumor mass, whilst the malignant

Hodgkin –Reed–Sternberg (HRS) cells are minimal(16). Each of the malignant and non-malignant cells secrete biomarkers, but it is still controversial to determine whether type of biomarkers could be the best monitoring tool of disease response and treatment efficacy. It has been reported that HRS related chemokines carry more specificity, whilst those related to the microenvironment are more sensitive(5). The cysteine-cysteine chemokineligand 17 (CCL 17), also named as thymus and activation regulated chemokine (TARC) is a specific biomarker to HRS cells. Therefore, TARC shows high specificity to HL patients. In addition, serial estimation of serum TARC levels can early determine the response to treatment, even after the first chemotherapeutic cycle(17-19). Furthermore, the anti-inflammatory M2 macrophages express the biomarker CD163. CD163 is reported to be elevated within the neoplastic node and in the serum of HL patients. Nevertheless, there is a paucity of clinical studies that evaluate CD163 for monitoring the disease response to treatment(20-23). Our study aims to investigate the prognostic utility of serum TARC, CD163 and Serum β2MG in patients with HL during and post therapy and measure the treatment response.

2. Methods

Patients

In this multicenter prospective observational study, we included 84 patients with HL from November 2015 till April 2016 in both Damietta Cancer Institute, Damietta, Egypt and OCMU Oncology Center, Mansoura University, Mansoura, Egypt. The included patients were patients, aged from 18 to 70 years, with recently diagnosed HL and were not involved in any chemotherapeutic treatment program. We omitted patients who were positive for Epstein–Barr virus (EBV), HIV, active hepatitis B or C, or auto-immune disease. Furthermore, we omitted patients with previous history of malignancy, previous treatment with immunosuppressive agents, or previous history of immunosuppression. The initial staging was conducted based on PET and CT scans. The included patients were treated by either AVBD (adryamicin bleomycin, vinblastine, and dacarbazine) alone or combined with either other chemotherapeutic agents (BEACOPP, DHAP, IGEV, and MINE) or involved-fieldradiotherapy (IFRT) based on the stage of the disease according to the institutional guidelines. From the included patients, five serial blood samples were taken; immediately pretreatment, after the second cycle, after the third cycle, one month after treatment, and six months after treatment. The complete response and partial response of the disease were defined according to the International Harmonization response criteria or the International Working Group response criteria (24, 25). This study was in compliance with the declaration of Helsinki and approved by the institutional review boards of both institutions. All participants signed informed consents at the beginning of the study.

Serum biomarkers assay

Under complete aseptic condition, 5 ml of peripheral venous blood was collected from each patient. The serum was stored at -80˚c until the completion of sample processing. Double-antibody sandwich ELISA was used for quantifying the serum level of both TARC and CD163. sTARC was quantified using the Human TARC ELISA kits (RayBiotech, Inc., Norcross, Georgia) while sCD163 was quantified using Quantikine Human CD163 ELISA kits (R & D Systems, Inc., Minneapolis, MN). Each biomarker was assessed according to the manufacturer's instructions. sCD163 was diluted into 1:20. On the other hand, β2MG was quantified using radioimmunoassay kit (Immunotech, Inc., Prague, Czech Republic) according to the manufacturer's instructions. In order to ensure the accuracy, double assessment was performed and the average was obtained.

Statistical analysis

All statistical analyses of the data were done by statistical package for the social sciences (SPSS), version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± SD, whereas categorical variables were expressed as numbers (percentages). A value of $P < 0.05$ was considered statistically significant. The main end point was the identification of patients with HL. The levels of markers were analyzed by analysis of variance (T-Test) but Chi-square test was done for independent samples. Overall Survival (OS) was defined as the time from diagnosis to death from any cause, or to time of last follow-up for patients who remained alive. The receiver operating characteristic (ROC) curve and area under curve (AUC) analysis was used to determine the sensitivity and specificity of each biomarker with the appropriate cutoff value. Furthermore, Kaplan–Meier analysis was used to estimate the OS.

3. Results

Patients characteristics

Among the included 84 patients with HL, the female to male ratio was 3:4, while the young (≤ 35 years) to older (> 35 years) patient ratio was 17: 25. The most frequent pathological subtype was nodular sclerosis, in 45 patients (53.5 %), followed by mixed cellularity that reported in 23 patients (27.3%). However, lymphocyte depletion was reported in 10 patients (9.5 %) and nodular lymphocyte predominant was reported in six patients (7.1 %). There were 52

patients (61.9 %) in the early stages (I, II) while 32 patients (38.1 %) were in the advanced stages (III, IV). Having the treatment, ABVD was the only treatment in 23 (38.1%) patients with 2-8 cycles. Combined ABVD with other chemotherapeutic options was the treatment in 42 (50%) patients, while combined ABVD with IFRT was used only with 10 patients. The disease response was complete in 34 (40.4 %) and partial in 48 (57.1 %) patients (Table 1).

Table 1. Clinicopathological characteristic of patients.

Clinical features		No	Percent
Number of the included patients		84	100%
Sex (male)		48	57.2 %
Age (>35 years)		50	59.5%
stages			
	I	38	45.2%
	II	14	16.7%
	III	28	33.3%
	IV	4	4.8%
pathology			
	Nodular sclerosis	45	(53.5%)
	Mixed Cellularity	23	(27.3%)
	Lymphocyte Depletion	10	(9.5%)
	Nodular Lymphocyte Predominant	6	(7.1%)
B-Symptoms		22	26.2 %
Disease response			
	Partial response	48	57.1 %
	complete response	34	40.4 %
Therapy type			
ABVD only			
	2 cycles	4	12.5%
	4 cycles	8	25.0%
	6 cycles	12	37.5%
	8 cycles	8	25.0%
	Total	32	38.1%
ABVD and/or other chemotherapy		42	50.0%
ABVD+RT		10	11.9%

Abbreviation, ABVD, adriamycin/bleomycin/vinblastine/dacarbazine; BEACOPP, bleomycin / etoposide / adriamycincyclophosphamide / vincristine / procarbazine / prednisone: DHAP, dexamethasone / highdoseara C / cisplatin; ICE, ifosfamide / carboplatin / etoposide;IGEV, ifosfamide / gemcitabine / vinorelbine / dexamethasone; MINE, mesna, ifosfamide, mitoxantrone, and etoposide; RT, radiotherapy.

Table 2. Deference between biomarkers regarding the clinicopathological characteristics of the patients.

variable		CD163			TARC			β2MG		
		mean	SD	P value	mean	SD	P value	mean	SD	P value
Pathology										
	Nodular Sclerosis	3.55	1.02	< 0.05	263.38	75.30	< 0.05	2.37	0.74	< 0.05
	Mixed Cellularity	3.82	1.20		257.04	78.21		2.68	0.39	
	Lymphocyte Depletion	3.79	1.18		235.30	69.71		2.03	0.27	
	Nodular Lymphocyte Predominant	3.33	1.04		204.13	68.92		1.98	0.61	
Ann prop stage										
	Early (I – II)	3.25	1.00	<0.001	206.61	65.83	<0.0001	2.00	0.52	<0.001
	Advanced (III-VI)	4.77	1.30		322.97	84.88		3.19	0.92	
Symptoms										
	B-Symptoms	4.87	1.09	<0.01	318.96	103.84	<0.001	3.83	1.16	<0.05
	No-symptoms	3.88	1.10		219.68	69.20		2.79	0.77	
Response										
	Partial response	4.83	1.21	<0.05	293.01	92.34	<0.01	3.47	1.02	<0.01
	Complete response	3.51	1.11		229.63	71.12		2.13	0.62	

CD163, cluster differentiation 163; TARC, Thymus and activation-regulated chemokine; β2MG, Beta 2 microglobulin

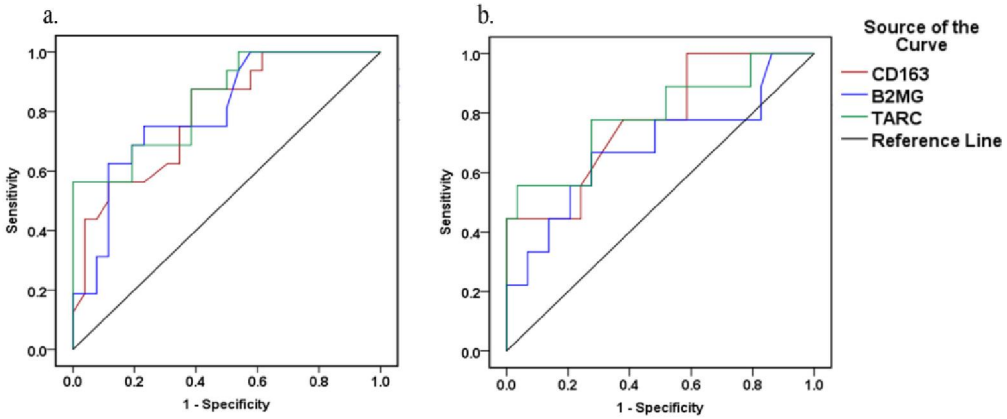

Figure 1. Receiver operating characteristics curve (ROC) and area under the curve (AUC) Highlighting the diagnostic performance (sensitivity and specificity) of TARC, CD163, and β2MG in determining the disease severity in the form of; late stages (a) or presence of B symptoms (b).

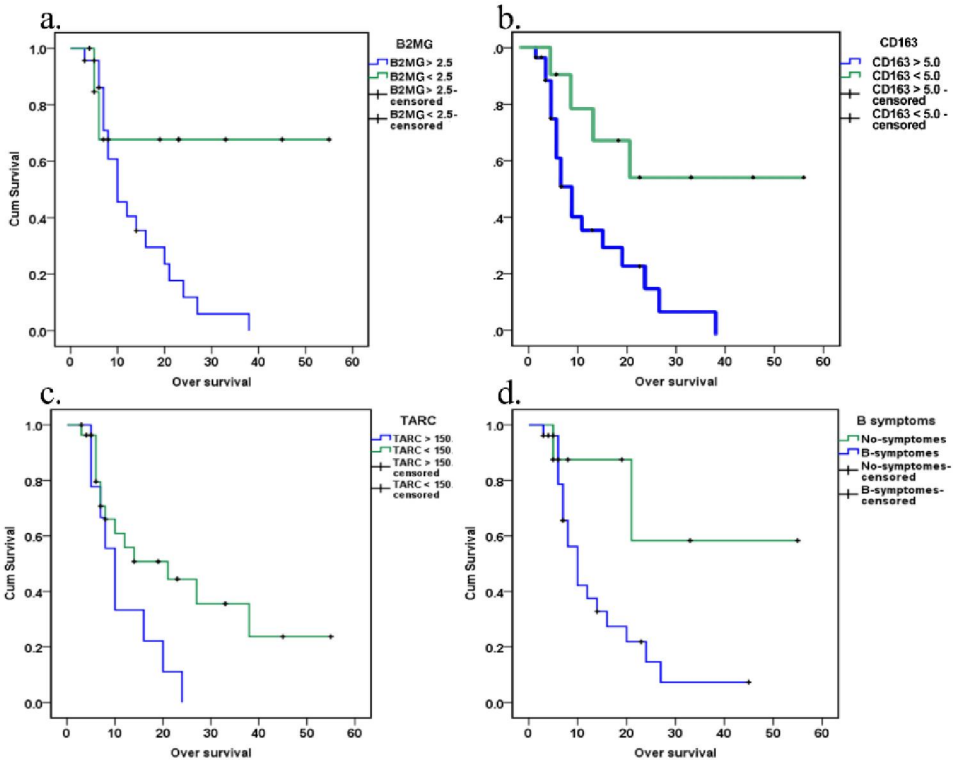

Figure 2. Kaplan–Meier curves for estimation of over survival (OS) in patients of Hodgkin lymphoma; a, OS with serum β2M concentrations < 2.5 mg/l and >2.5 mg/l at prognosis; b, OS with serum CD163 concentrations<5.0 ng/ml and >5.0 ng/ml at prognosis; c, OS with serum TARC concentrations < 150 ng/l and >150 ng/l at prognosis; d, OS regarding the presence of B symptoms at the diagnosis.

Severity determination

Having the pathology, there were significant differences between nodular sclerosis, mixed cellularity, lymphocyte depletion, and nodular lymphocyte predominant regarding the level of either TARC, CD163, or β2MG at the baseline (P< 0.05 in all). Similarly, there was a high significant difference between early and advanced stages regarding the baseline of these three biomarkers (P<0.001 in all). Furthermore, the levels of these biomarkers were

significantly higher in patients with B symptoms than patients without B symptoms ($P< 0.05$ in all). Moreover, the partial disease response was associated with higher values of these three biomarkers than the complete disease response ($P< 0.05$ in all) (Table 2).

Supportingly, the ROC analysis showed that TARC, CD163, and β2MG had high diagnostic values in highlighting the advanced stages (AUC = 0.84; P value <0.001, AUC = 0.79; p value <0.001, and AUC = 0.78; p value <0.001, respectively). TARC showed the highest specificity (80.8%) followed by β2MG (76.9%) then CD163 (70.0%), while β2MGshowed the highest sensitivity (75.0%) followed by TARC (68.8%) then CD163 (62.5%). The optimal cutoff value for TARC was 150 ng/l that yield 77.8% sensitivity and 72.4% specificity. Regarding the CD163, the optimal cutoff value was 5.0 ng/ml that yield 76.7% sensitivity and 70.0% specificity. Similarly, β2MG displayed 66.7% sensitivity and 72.4% specificity with 2.50 mg/l as optima cutoff value (Figure 1).

Assessment of the disease response

The Kaplan Meier analysis showed that β2MG was associated with best survival function as patients with β2MG<2.5 mg/l were more prone to favored disease response than patients with β2MG<2.5 mg/l (P<0.001). Similarly, CD163 has shown good prognostic function and disease response prediction. Patients with CD163 <5.0 ng/ml were more prone to disease response than patients with CD163>5.0 ng/ml (P<0.001). Furthermore, TARC was associated with best survival function as patients with TARC <150 ng/l were more prone to favored response than patients with TARC>150 ng/l (P<0.04). Interestingly, presence of B symptoms can also predict the prognosis of and the disease response as absence of B symptoms was associated with better survival than presence of B symptoms (Figure 2).

4. Discussion

Precise diagnosis and meticulous prediction of the prognosis of each patient with HL is crucial for determining the optimal treatment strategy. Our study revealed that serum TARC, CD163 and Serum β2MG are of high diagnostic and prognostic values through predicting the severity and disease response. The HRS cell specific TARC is a highly specific biomarker for cHL disease activity (26, 27). In about 85% of patients, TARC is detectable and elevated in the serum at the diagnosis and before the treatment. Supportingly, previous studies showed that the pre-treatment serum TARC levels significantly correlated with stages of the disease, metabolic activity, and erythrocyte sedimentation rate (18). Moreover, any changes in TARC levels during chemotherapy may be a biomarker for treatment response evaluation (28). These results, in addition to the results of Plattel et al (29), supports our results that highlighted the accuracy of TARC in predicting the severity of the disease and the treatment response. Therefore, TARC may be used as a cancer-specific serum biomarker for defining diagnosis and prognosis of HL. Moreover, there is an increasing interest on the amount of tumor associated macrophages (TAM) infiltration in the tumor microenvironment. The amount of TAM is strongly associated with not only shortened survival but also the likelihood of relapse for disease-specific survival(22). The functional characterization of TAM is still to be performed. Possibly, differences in survival among patients could be explained by the macrophages M1/M2 binary, on which these cells differentiate. Furthermore, the M2 macrophage marker soluble CD163 is elevated in serum of patients with HL(28, 30). Unlike M1 macrophages, M2 macrophages prompt tumor cell growth and metastasis (31). CD163 is currently investigated as an additional biomarker of macrophage infiltration in HL microenvironment and its increased level is associated with poor outcome, and a rise in the treatment-related deaths with poor survival rate (23). Recently, the circulating fraction of CD163 in serum has been evaluated in patients at diagnosis and relapse, showing that it is not inferior to TARC to identify patients with poor outcome. Moreover, several studies demonstrated that elevated CD163 expression correlates with advanced cancer stages, unfavorable prognosis, early distant recurrence, and reduced patient survival in various types of cancers, including HL(32).

Noticeably, CD163 not only exists as a membrane-bound form, but also presents as a soluble form in plasma and other tissue fluids. The M2 macrophage soluble CD163 is elevated in serum of patients with HL. Furthermore, serum CD163 has been reported to be elevated in several inflammatory conditions, such as sepsis, diabetes, liver cirrhosis, rheumatoid arthritis, human immunodeficiency virus and macrophage activation syndrome(33). Nevertheless, this does not explain the different patterns observed in plasma versus serum samples. Interestingly, a correlation has been found between CD163 and interim response. It is worthy that complete remission and partial remission are greatly overlapped. Jones et al showed a gradual decrease of sCD163 during and after treatment in serum samples of classical HL patients(28). We observed a similar pattern in our serum samples, while the plasma samples showed a slight post-treatment rise in soluble CD163 levels. This increase might reflect treatment-induced inflammatory responses. This makes CD163 less useful as a biomarker for response evaluation at the individual patient level(28). However, our study revealed that soluble CD163 level was significantly

correlated with disease severity and response to treatment. Our result is supported by the results of Plattel et al who reported a significant correlation between CD163 and the presence of B symptoms (29).

On the other hands, the initial level of β2MG has been also confirmed to be an important diagnostic biomarker in most lympho-proliferative diseases in adults, including HL. Our results support the previous results revealing high correlation between serum β2MGand either Ann Arbor stage, the presence of B symptoms, or unfavorable prognosis (34). In accordance with our results, Nakajima et al demonstrated that the ROC curve analysis showed that the appropriate cutoff of serum β2MG levels is 2.5 mg/L for predicting the overall survival. It is also estimated that serum β2MG had a tendency to be significantly associated with age more than 45 years and Ann Arbor stages III–IV(35). By virtue of such biomarkers, HL has changed its prognosis from being relatively incurable to one in which patients have a high likelihood of long-term survival (36).

In patients with advanced-stage HL, the early response after two courses of ABVD chemotherapy, when evaluated with 18 FDG-PET scan, showed important prognostic significance (37). It has been reported that the complete response has a rate of 73-89%, whilst the 5-year freedom from progression rate is 73-76%. In addition, the 5-year overall survival rate reached up to 90% in intermediate and advanced stage HL(38).

5. Conclusion

Our study highlighted that serum TARC and CD163 may serve as good prognostic biomarkers for follow up of HL, particularly in the absence of B symptoms. Serial TARC measurements accurately reflected disease activity and correlated with clinical treatment response at the individual patient level. Moreover, CD163 was found to be elevated in HL patients. Furthermore, the levels of TARC, CD163, and β2MG were reported to be highly associated with the disease severity. The combination of CD163, TARC, andβ2MGmay significantly improve the prognostic value of HL than that of β2MG alone. Therefore, further studies investigating the roles of the combination of these three biomarkers in both diagnosis and prognosis are needed.

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3/25/2019