Serum thymus and activation-regulated chemokine (TARC) levels in newly diagnosed patients with Hodgkin lymphoma: a new promising and predictive tool? Preliminary report

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Abstract
Thymus and activation-regulated chemokine (TARC) is expressed on Reed-Sternberg cells of patients with classical Hodgkin lymphoma (HL) and may serve as a marker in response assessment. In our study, we correlated serum TARC levels with early response to treatment measured by PET/CT in 19 newly diagnosed patients with HL who received ABVD (Adriblastin, Bleomycin, Vinblastine, Dacarbazine) regimen. Finally, 17 patients were analyzed and six of them (35%) achieved PET/CT negativity defined as Deauville (D) 1 or 2 after 2 cycles of ABVD; 11 pts (65%) had D3 on PET/CT. None of the patients presented D 4/5. Median serum TARC levels at diagnosis were significantly higher when compared with healthy controls: 5718 pg/ml vs 76.1 pg/ml ($p < 0.001$). All study patients were treated with ABVD regimen and there was a significant decrease of baseline serum TARC levels after 2 cycles of therapy. No significant difference of baseline serum TARC levels was demonstrated between patients with D1/2 and D3 whereas levels were significantly decreased after 2 cycles of ABVD in patients D1/2 vs D3; $p = 0.049$. There was a tendency to higher baseline serum TARC levels in patients with an increased LDH (lactate dehydrogenase) activity ($p = 0.08$) and in those who progressed when compared with those who maintained response ($p = 0.09$). Serum TARC levels decrease after chemotherapy and may serve as a marker of response assessment.

Keywords Hodgkin lymphoma · Thymus and activation-regulated chemokine · Chemotherapy · Response

Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| ABVD         | Adriblastin, Bleomycin, Vinblastine, Dacarbazine |
| CR           | Complete remission |
| GHSG         | German Hodgkin Study Group |
| Hgb          | Hemoglobin |
| HL           | Hodgkin lymphoma |
| IPS          | International Prognostic Score |
| LD           | Lymphocyte depleted |
| LDH          | Lactate dehydrogenase |
| LR           | Lymphocyte rich |
| MC           | Mixed cellularity |
| NS           | Nodular sclerosis |
| PET/CT       | Positron emission tomography/computed tomography |
| pg/ml        | Picogram/milliliter |
| PLT          | Platelets |
| PR           | Partial respond |
| p-value      | Probability value |
| RS           | Reed-Stenberg |
| Th2          | T-helper type 2 |
| WBC          | White blood cells |

Introduction

Hodgkin lymphoma (HL) accounts for approximately 10% of all lymphomas. It usually affects younger people at median age between 20 and 30 years. There are two variants of HL: classical and non-classical; the former is more commonly observed. Histologically, classical HL is characterized by the presence of Reed-Sternberg (RS) cells, which reside in an extensively inflammatory tumor microenvironment.

HL remains a potentially curable malignancy; however, despite the availability of different treatment modalities...
including chemo- and radiotherapy, ~20% of treated patients do not achieve a long-term response [3]. On the other hand, some patients, especially those with a less advanced disease, can be cured using fewer intensive therapies. Of note is, that factors which may predict a response to treatment and thereby influence the intensity of administered therapy have not been identified so far. The Ann Arbor staging system based is used to assess the extent of disease involvement and is commonly used in daily clinical practice. Several laboratory and clinical parameters are found to be helpful in risk assessment and treatment stratification [1, 5, 6]; however, none of them serves as a marker in treatment response. Thymus and activation-regulated chemokine (TARC) is a chemokine involved in lymphocyte migration. TARC binds to chemokine receptors C–C chemokine receptor type 4 (CCR4) and displays activity for T lymphocytes. It is expressed in the thymus and also on keratinocytes, vascular endothelial, and dendritic cells. Moreover, it is highly expressed on the surface of Reed-Sternberg cells [6, 10, 12]. Increased serum TARC level seems to play a role in survival and proliferation of Reed-Sternberg (RS) cells [13]. Some other studies demonstrated that TARC may be helpful in disease response and prognosis [11, 12].

In our study, we present our preliminary results focusing on potential correlation between serum TARC level and treatment response measured by PET/CT (positron emission tomography/computed tomography) in HL patients who received ABVD (Adriblastin, Bleomycin, Vinblastine, Dacarbazine) regimen.

**Material and methods**

Nineteen patients (74% of women) with newly diagnosed classical HL were included in this prospective study. A vast majority of patients was diagnosed with nodular sclerosis (NS) histological subtype and less than 50% of them manifested B symptoms. Nine patients (out of 12) who were classified as Ann Arbor stage II had at least 1 adverse risk factor according to the GHSG (German Hodgkin Study Group) classification [9]. Seven patients were diagnosed at III–IV disease stage; 2 of them displayed more than 2 risk factors. Two patients were excluded from the final analysis due to low quality of the samples.

The patients’ characteristics at study entry are shown in Table 1. The patients included in the analysis were free

| Table 1 Clinical characteristics of patients included in the study |
|-----------------|-----------------|-----------------|
| Variable                | Patients N = 19 | Control group N = 20 |
| Age (years) at diagnosis (median) (range) | 24 (20–70) | 28 (23–65) |
| Female, n (%)         | 14 (74) | 15 (60) |
| Histological type of HL, n (%) | 15 (79) | - |
| NS                   | 4 (21) | - |
| MC                   | 8 (42) | - |
| B symptoms, n (%)     | 8 (42) | - |
| Ann Arbor stage at diagnosis, n (%) | 0 (0) | - |
| I                    | 12 (63) | - |
| II                   | 3 (16) | - |
| III                  | 4 (21) | - |
| IV                   | 13/6 | - |
| WBC [10⁹/L] median (range) | 9.4 (5.5–17.6) | - |
| Hgb [g/dl] median (range) | 12.4 (8.9–16) | - |
| PLT [10⁹/L] median (range) | 329 (200–866) | - |
| > 3 involved lymph node areas yr/n | 13/6 | - |
| Stage II (GHSG); n = 12 | 3 (25) | - |
| Favorable; n (%)       | 9 (75) | - |
| IPS for stage III and IV; n = 7 | 5 (71) | - |
| Low risk 0–2 n (%)    | 2 (29) | - |
| High risk 3–7 n (%)   | 2 (29) | - |

HL: Hodgkin lymphoma, NS: nodular sclerosis, MC: mixed cellularity, Hgb: hemoglobin, WBC: white blood cells, PLT: platelets, GHSG: German Hodgkin Study Group, IPS: International Prognostic Score, y: yes, n: no
of chronic viral infections and other disorders which could affect the results. All patients were performed PET/CT at baseline and then after 2 cycles of ABVD regimen (interim PET/CT). PET/CT assessment was then repeated at the end of treatment, 3 weeks after the last cycle of ABVD (Adriamycin 35 mg/m², Bleomycin 10 mg/m², Vinblastine 6 mg/m², Dacarbazine 375 mg/m² on days 1 and 15). The response was evaluated according to criteria published elsewhere [8]. The control group included subjects who were age- and sex-matched.

Serum TARC levels were assessed at diagnosis — before chemotherapy (first sample) and after two cycles of ABVD (second sample). All serum samples were obtained from centrifuged blood samples and then frozen at −180 °C. TARC levels were measured using commercially available ELISA (enzyme-linked immunosorbent assay) according to the manufacturer’s instructions (R&D System, Wiesbaden, Germany). The cut-off point was set at the TARC levels above 800 pg/ml according to data published elsewhere [4, 10, 11]. The minimal detectable serum level of TARC was 1.0 pg/ml.

**Statistical analysis**

Nonparametric comparisons of group means were performed by using the Mann–Whitney U test. Proportions were compared by Fisher’s exact test. Correlations were performed using Spearman’s rank sum. A p-value less than 0.05 was considered significant. All computations were performed with StatSoft Poland analysis software (version 10.0).

**Results**

Seventeen patients were included in the final analysis. Median serum TARC levels at diagnosis were significantly higher if compared with healthy controls: 5718 pg/ml (range 3173–6952) vs 76.1 pg/ml (range 32.2–243.3); p < 0.001. There was a significant decrease of baseline serum TARC levels after 2 cycles of ABVD: 5718 pg/ml (range 3173–6952) vs 456 pg/ml (range 70–539); p < 0.001. There was also no significant difference of baseline serum TARC levels between patients with bulky and non-bulky disease; 5628 pg/ml (range 3173–6943) vs 5373 pg/ml (range 3173–6939). There was also no significant difference of baseline serum TARC levels between patients with an increased LDH (lactate dehydrogenase) activity when compared with those with normal LDH activity: p = 0.08 and in those who progressed when compared with those who maintained response: median 6143 pg/ml (range 3173–6952) vs 4855 pg/ml (range 3812–6943); p = 0.09.

There was no significant difference of baseline serum TARC levels between stages II (n = 11) and III–IV (n = 6): median 5608 pg/ml (range 3812–6952) vs 5853 pg/ml (range 3173–6939). There was also no significant difference of baseline serum TARC levels between patients with bulky and non-bulky disease; p = 0.55. Baseline serum TARC levels did not correlate with the presence of B symptoms; p = 0.84, and number of involved lymph nodal areas; p = 0.1. There was also no statistical difference between IPS 0–2 and IPS > 2; p = 0.27 (Table 2).

**Discussion**

TARC was identified as a chemokine that activates T-helper type 2 (Th2) cells [13]. Recent studies have demonstrated that T cells surrounding RS cells in patients with HL present a Th2 pattern. Interestingly, other lymphomas do not express TARC. Baseline TARC level was found to be associated with tumor burden and its early reduction after 2 cycles of ABVD in patients with bulky and non-bulky disease.

**Table 2** Correlation between serum TARC levels at baseline and selected parameters

| Variable                     | Median TARC level [pg/ml] | p-value |
|------------------------------|---------------------------|---------|
| Stage I–II                   | 5608                      | 0.44    |
| Stage III–IV                 | 5853                      |         |
| Bulky disease                | 5628                      | 0.55    |
| Non-bulky disease            | 5373                      |         |
| Increased LDH activity       | 6695                      | 0.08    |
| Normal LDH activity          | 4638                      | 0.84    |
| B symptoms present           | 5470                      | 0.27    |
| B symptoms absent            | 4888                      |         |
| IPS 0–2                      | 4947                      |         |
| IPS > 2                      | 6121                      |         |
| Interim PET/CT D1–D2         | 5028                      | 0.88    |
| Interim PET/CT D3            | 5826                      |         |

pg picograms, ml milliliters, p-value probability value, IPS International Prognostic Score, LDH lactate dehydrogenase, PET/CT positron emission tomography/computed tomography, D Deauville
after chemotherapy may correlate with treatment efficacy [10–12].

In our study, we demonstrated an increased baseline serum TARC levels (>800 pg/ml) in most patients with HL and this finding was in line with other reports [4, 11]. In one of the previous studies, patients at stage I had lower baseline serum TARC level when compared with more advanced stages [12]. We have also demonstrated that serum TARC levels in HL patients were significantly elevated when compared with healthy controls. It was demonstrated that increased serum TARC levels are indicative of an active disease [11, 12]. It seems that serum TARC level may serve as a marker of response assessment because its significant reduction was observed in patients who achieved response to therapy [4, 7, 11, 12].

Moreover, it was shown that increased serum TARC levels (>2000 pg/ml) maintained after treatment correlated with worse survival, higher risk of progression, or disease relapse [12]. We have shown a significant reduction of serum TARC level after two cycles of ABVD when compared with baseline and it correlated with the results of PET/CT results. There was a significant difference in serum TARC levels after 2 cycles of chemotherapy depending on PET/CT results measured by the Deauville scale. Similar results were also reported by others — chemo-responsive patients showed a significant decrease of serum TARC levels as early as after the first cycle of chemotherapy [10]. Of note is, that in one patient from our study, serum TARC levels did not decrease below the cut-off point and this patient was found to have D3 on interim PET/CT with subsequent disease progression. One of the previous studies has shown that patients with permanently increased serum TARC levels and interim PET/CT (+), defined as D4-D5, have a poor prognosis [2]. We have also confirmed that patients with interim D3 had the significant serum TARC levels higher than those with D1–2.

Jones et al. have also demonstrated that persistence of elevated serum TARC levels in patients who achieved a clinical response to therapy may correlate with subsequent disease progression [7]. It seems that the TARC serum level is not only a marker of treatment response, but may also play a role as a predictive factor. One can not exclude that patients with elevated TARC levels after therapy can benefit from earlier treatment escalation.

In contrary to other studies, we did not demonstrate a correlation between serum TARC levels and the presence of B symptoms and other well-established risk factors including disease stage at diagnosis [11, 12]. It was probably due to low number of included patients. Moreover, the majority of our patients was diagnosed at stage II (63%). On the other hand, earlier studies have demonstrated significantly elevated serum TARC levels in most HL patients irrespective of disease stage [2, 4]. It may suggest that TARC may serve as a marker of both disease activity and response assessment [2].

To conclude, our study seems to confirm that the presence of significantly elevated serum TARC levels in patients with newly diagnosed HL compared with matched healthy controls. In line with other studies, we have demonstrated a significant reduction of serum TARC levels after chemotherapy. Serum TARC level may serve as a new diagnostic marker along with the results of interim PET/CT. The new predictive markers are highly required to individualize therapeutic approach in order to avoid overtreatment and minimize side effects. Nevertheless, further studies are needed to confirm the predictive role of TARC in HL.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments.

Competing interests The authors declare no competing interests.

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