# Plasma thymus and activation-regulated chemokine as an early response marker in classical Hodgkin's lymphoma

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## ABSTRACT

**Background**

Plasma thymus and activation-regulated chemokine is a potential biomarker for classical Hodgkin's lymphoma. To define its value as a marker to monitor treatment response, we correlated serial plasma thymus and activation-regulated chemokine levels with clinical response in newly diagnosed and relapsed classical Hodgkin's lymphoma patients.

**Design and Methods**

Plasma was collected from 60 (39 early stage and 21 advanced stage) newly diagnosed classical Hodgkin's lymphoma patients before, during, and after treatment, and from 12 relapsed patients before and after treatment. Plasma thymus and activation-regulated chemokine levels were determined by enzyme-linked immunosorbent assay and were related to pre-treatment metabolic tumor volume, as measured by quantification of 2-[18F]fluoro-2-deoxyglucose positron emission tomography images, and to treatment response.

**Results**

Baseline plasma thymus and activation-regulated chemokine levels correlated with stage of disease and bulky disease, and more closely with metabolic tumor volume. Response to treatment was observed among 38 of 39 early stage and 19 of 21 advanced stage patients. Reduction in plasma thymus and activation-regulated chemokine to normal range levels could be observed as early as after one cycle of chemotherapy in all responsive patients, while plasma levels remained elevated during and after treatment in the 3 non-responsive patients. Plasma thymus and activation-regulated chemokine was elevated in all 12 relapsed patients at time of relapse and remained elevated after salvage treatment in the 4 non-responsive patients.

**Conclusions**

Baseline plasma thymus and activation-regulated chemokine levels correlate with classical Hodgkin's lymphoma tumor burden and serial levels correlate with response to treatment in patients with classical Hodgkin's lymphoma.

Key words: Hodgkin's lymphoma, plasma thymus, chemokine, tumor burden, serial plasma.

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## Introduction

In classical Hodgkin's Lymphoma (cHL), the neoplastic Hodgkin Reed-Sternberg (HRS) cells are vastly outnumbered by cells in the surrounding reactive infiltrate. This infiltrate is of major importance for the proliferation and survival of HRS cells. Different chemokines and cytokines produced by HRS cells and cells in the reactive infiltrate are responsible for the formation and maintenance of this reactive environment.[1-4]

The CC chemokine ligand 17 (CCL17) or Thymus and Activation-Regulated Chemokine (TARC) is highly expressed by HRS cells in cHL, but not by the tumor cells of nodular lymphocyte predominant Hodgkin's lymphoma or other B-cell derived non-Hodgkin's lymphomas.[5,6] TARC binds specifically to the CC chemokine receptor 4 (CCR4). CCR4 is mainly expressed on regulatory T and Th2 cells that are both abundant in the reactive infiltrate of cHL.[6-8] Approximately 90% of the cHL patients show positive TARC staining in HRS cells by immunohistochemistry (IHC) and about 85% have significantly elevated levels of TARC in their pre-treatment serum or plasma sample compared to healthy controls.[9,10] Although patients with active atopic diseases can also have elevated plasma TARC levels, this is only a modest elevation which is in a significantly lower range than the high plasma TARC levels observed in cHL.[11] Pre-treatment serum TARC levels correlate with stage of disease, erythrocyte sedimentation rate, and leukocyte and lymphocyte counts in cHL.[9,10] Niens *et al.*[9] reported TARC levels within the normal range after successful treatment in 7 cHL patients and persistent elevated TARC in a single non-responsive patient. Weihrauch *et al.*[10] reported diminished survival rates among patients with higher TARC levels after treatment. However, nothing is known about TARC dynamics during treatment in relation to clinical treatment response.

We, therefore, prospectively collected serial plasma samples from newly diagnosed and relapsed cHL patients. The aim of the current study was to correlate plasma TARC levels with tumor burden at time of diagnosis, and to correlate serial plasma TARC levels during and after treatment with cHL treatment response.

## Design and Methods

### Patient inclusion and treatment

Serial plasma samples were prospectively collected from all newly diagnosed and relapsed cHL patients treated at the University Medical Center Groningen (UMCG) from January 2006 until June 2011.

Inclusion criteria for both newly diagnosed and relapsed cHL patients were: i) receiving standard treatment regimens; ii) availability of a plasma sample before start of treatment and one or more plasma samples during or after treatment; and iii) confirmation of TARC expression in diagnostic tissue by immunohistochemistry or by elevated baseline plasma TARC if diagnostic tissue was not available. From 78 newly diagnosed patients treated in the UMCG, 18 were excluded: one patient refusal, 2 were receiving palliative treatment, 9 lacked a pre-treatment plasma sample, 3 had negative tissue TARC staining, and 3 had no available tissue and normal pre-treatment plasma TARC levels. The total study cohort was, therefore, made up of 60 patients. From 17 relapsed patients, 12 patients eligible for DHAP salvage treatment followed by autologous stem cell transplantation were included, while 5 patients were excluded (4 were receiving only palliative treatment and one lacked a plasma sample after treatment).

Permission for this study was obtained from the institutional review board of the UMCG and all participating patients and healthy controls gave their signed informed consent. Routine staging of patients at diagnosis or at relapse included diagnostic Computer Tomography (CT) imaging, 'whole body' 2-[18F]fluoro-2-deoxyglucose positron emission tomography (FDG-PET) imaging, and bone marrow biopsy. Presence of bulky disease was defined as presence of a mediastinal mass greater than one-third of the thoracic diameter on chest X-ray (on level Th5-Th6) and/or a nodal mass of more than 10 cm CT imaging. Response to treatment was evaluated according to the revised International Working Group response criteria.[12] Evaluation included FDG-PET/CT scanning which was interpreted according to the International Harmonization Project criteria (IHP).[13] In the vast majority of patients, FDG-PET/CT scanning was performed using a Siemens Biograph PET/CT mCT 64 scanner.

Patients were treated according to European Organisation for Research and Treatment of Cancer (EORTC) clinical trial protocols. Table 1 shows patients' characteristics and data on chemo- and radiotherapy regimens. Briefly, standard treatment for stage I/II (early stage) patients consisted of 3-6 cycles of ABVD chemotherapy with or without 30-36 Gy involved node radiotherapy (IN-RT) according to the EORTC (20051) H10 trial.[14] Standard treatment for stage III/IV (advanced stage) patients consisted of 6-8 cycles of ABVD without radiotherapy, or in cases participating in the EORTC 20012 trial, patients were randomized between 8 cycles of ABVD and 4 cycles of escalated BEACOPP (eBEACOPP) followed by 4 cycles of base-line BEACOPP.[15] Patients not enrolled in these clinical trials received conventional treatment, which is similar to the standard arm of these trials.

In the relapsed cohort, all patients were scheduled for DHAP-VIM-DHAP salvage chemotherapy, followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) in cases of at least a partial response on salvage re-induction. Three patients who were non-responsive to DHAP received second salvage chemotherapy consisting of 2 cycles of mini-BEAM before receiving ASCT (Table 1).

### Tissue and plasma collection

Diagnostic formalin fixed paraffin embedded tissue samples were retrieved from the tissue banks of the pathology departments of the UMCG and other regional pathology laboratories affiliated with the hospitals from which the patients were referred for treatment (Martini Hospital Groningen, Sazinon Hoogeveen, Isala Klinieken Zwolle, SSZOG Winschoten and Pathology Friesland Leeuwarden. Immunohistochemistry for TARC was performed to confirm expression of TARC by Hodgkin tumor cells. Immunohistochemistry was performed on formalin fixed paraffin embedded tissue samples mounted on 3-aminopropyltriethoxysilane (APES) coated slides using a goat anti-human TARC antibody (R&D Systems, Minneapolis, USA) after heat-induced antigen retrieval. Ninety-four percent of analyzed tissue samples were positive for TARC. Patients with TARC negative tumor cells also had low plasma TARC at diagnosis and were excluded (*see above*).

In the newly diagnosed patients, plasma was collected at diagnosis (baseline), after one cycle of chemotherapy, at mid-treatment and after completion of first-line treatment and during routine follow up. Mid-treatment was after 2 cycles of ABVD in early stage patients and after 4 cycles of ABVD or eBEACOPP in advanced stage patients, in parallel with formal response evaluation by FDG-PET/CT. In the relapsed patients, plasma samples were collected before and after salvage treatment. In addition, plasma samples

were collected from 107 age- matched (median 31, range 19-62 years) and sex- matched (57% female) healthy controls.

### Plasma TARC analysis

Ten mL of blood was collected in ethylenediaminetetraacetic acid (EDTA) tubes at each time point. Plasma was obtained after centrifugation at 900 x g and stored in aliquots at -20°C. TARC levels were measured by a double antibody sandwich ELISA (R&D systems, Minneapolis, USA). To reduce variation we used mass-calibrated standards and analyzed samples retrieved from a single patient simultaneously. Samples were analyzed without prior knowledge of patient identity or treatment results. To minimize a potential influence of active atopic diseases, we set the cut off for elevated plasma TARC levels at 1,000 pg/mL.

### Determination of metabolic volume

Baseline FDG-PET studies performed at the University Medical Center Groningen were used for the determination of the pre-treatment metabolic volume. Reconstruction of the FDG-PET studies was performed according to the Netherlands protocol for standardization of FDG whole body PET studies.[16] The four sites with the most intense visual FDG uptake were selected as regions of interest (ROI). All ROIs were analyzed for the maximum Standard Uptake Value (SUVmax) and the corresponding metabol-

ic volume at a fixed threshold of 70% of the SUVmax. The total metabolic volume was calculated by adding up the volumes of the ROIs. All scans were analyzed without knowledge of plasma TARC levels.

### Statistics

We used non-parametric analyses because of the skewed distribution of the plasma TARC levels. Baseline plasma TARC levels were correlated to Ann Arbor stage of disease, presence of bulky disease, metabolic volume and SUVmax. Differences in plasma TARC levels between categorical variables were analyzed using the Mann-Whitney U test. Linear correlation coefficients (r) between plasma TARC levels and the metabolic volume were determined using Spearman's rank correlation test. All statistical analyses were performed using SPSS 16.0.

## Results

### Patients' characteristics

Basic characteristics and treatments of the 60 newly diagnosed (39 early stage and 21 advanced stage) and 12 relapsed cHL patients are summarized in Table 1. Median age among the newly diagnosed patients was 33 years (range 16-75) with slightly more females than males. Most patients had nodular sclerosis subtype.

### Baseline plasma TARC levels and tumor burden in newly diagnosed patients

Baseline plasma TARC was elevated (>1,000 pg/mL) in 55 out of 60 newly diagnosed patients (92%) and was significantly higher in cHL patients (median 28,013; range 69-269,048 pg/mL) compared to healthy controls (median 118 pg/mL, range 7-470; $P<0.001$; Figure 1).

Significantly higher levels of baseline plasma TARC levels were observed in patients with stage II-IV disease compared to patients with stage I disease ($P<0.001$, Figure 2A), as well as in patients with bulky disease compared to patients without bulky disease ($P=0.02$, Figure 2B). Baseline plasma TARC levels directly correlated with the metabolic FDG-PET volume (r=0.61, $P<0.001$, Figure 2C) and not with IPS score or presence of B symptoms.

Table 1. Patients' characteristics and treatment.

| | Newly diagnosed cHL patients (n=60) n. (%) | Relapsed cHL patients (n=12) n. (%) |
|---|---|---|
| Median age (range) | 33 (16-66) | 47 (25-64) |
| Female | 36 (60) | 5 (42) |
| Histology | | |
| Nodular sclerosis | 42 (70) | 10 (83) |
| Mixed cellularity | 4 (7) | 2 (17) |
| Lymphocyte rich | 3 (5) | - |
| cHL NOS | 11 (18) | - |
| Ann Arbor stage | | |
| I-II (early stage) | 39 (63) | 3 (25) |
| III-IV (advanced stage) | 21 (39) | 9 (75) |
| B symptoms present | 25 (42) | 4 (33) |
| Bulky disease | 22 (37) | 1 (8) |
| Treatment stage I/II patients (n=39): | | |
| ABVD 3-4 cycles + IN-RT | 26 (67) | - |
| ABVD 4-6 cycles | 11 (28) | - |
| ABVD 2 cycles, EscBEACOPP 2 cycles + IN-RT | 2 (5) | - |
| Treatment stage III/IV patients (n=21): | | |
| ABVD 6-8 cycles | 15 (71) | - |
| BEACOPP 5 cycles | 1 (5) | - |
| EscBEACOPP 4 cycles, BEACOPP 4 cycles | 5 (24) | - |
| Treatment relapsed patients (n=12): | | |
| DHAP-VIM-DHAP + BEAM+ ASCT | - | 9 (75) |
| DHAP-VIM-Mini-BEAM (2x) +BEAM + ASCT | - | 3 (25) |

*cHL: classical Hodgkin's Lymphoma; NOS: not otherwise specified; ABVD: adriamycin-bleomycin-vinblastine-dacarbazine containing chemotherapy regimen; IN-RT: involved node radiotherapy; BEACOPP: bleomycin-etoposide-adriamycin-cyclophosphamide-vincristine-procarbazine-prednisone containing chemotherapy regimen; eBEACOPP: escalated (dose intensified) BEACOPP; DHAP: dexamethason-citarabine-cisplatin containing salvage re-induction regimen; VIM: etoposide-ifosfamide-methotrexate containing regimen; ASCT: autologous stem cell transplantation; BEAM: carmustine-etoposide-cytarabine-melphalan myeloablative chemotherapy.*
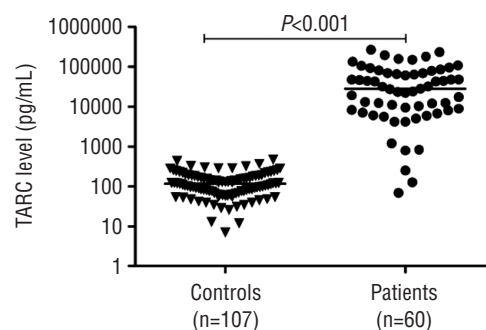


**Figure 1.** TARC expression in plasma from newly diagnosed cHL patients and healthy controls. Plasma TARC levels among 107 healthy controls and 60 pre-treatment newly diagnosed cHL patients. The median plasma TARC level was 118 pg/mL (range: 7-470) and 28,013 pg/mL (range 69–269,048) in the healthy controls and the cHL patients', respectively. Pre-treatment patient samples were significantly higher compared to the healthy controls (**P<0.001**).

### Plasma TARC as a response marker in early stage patients

Of 39 newly diagnosed patients with early stage disease, 37 achieved a complete response (CR), one a partial response (PR; UPN 38) and one had progressive disease (PD; UPN 39). In all patients with a CR, reduction in plasma TARC levels could be observed as early as after one cycle of chemotherapy (Figure 3 and *Online Supplementary Table S1*). Thirty-one of 37 patients with a final CR already had a CR at mid-treatment. The other 6 patients (of whom 2 with bulky disease) had a PR at mid-treatment, while TARC levels were already low after one cycle of chemotherapy. Thirty-six out of 37 patients with a CR had a continuous remission (median follow up 33 months, range 6-66). One patient (UPN 4) relapsed at 27 months follow up with concomitant re-elevation of plasma TARC.

The single patient with a PR at end of treatment (UPN 38) also showed a reduction of plasma TARC to normal range levels after one cycle of chemotherapy. This patient did not receive additional therapy and remained limited FDG-PET positive at serial post-treatment imaging studies but did not progress (21 months of follow up).

In the patient with PD (UPN 39), plasma TARC was persistently elevated during and after treatment. After progression during salvage chemotherapy, this patient died of progressive lymphoma.

### Plasma TARC as a response marker in advanced stage patients

Of 21 patients with advanced stage disease, 18 patients had a CR, one a PR (UPN 58) and 2 had PD (UPN 59 and 60). Similar to early stage patients, reduction in plasma TARC was significant after one cycle of chemotherapy in all CR patients (Figure 3B and *Online Supplementary Table S2*). Seventeen of 18 patients with a final CR already had a CR at mid-treatment and one patient with a final CR had
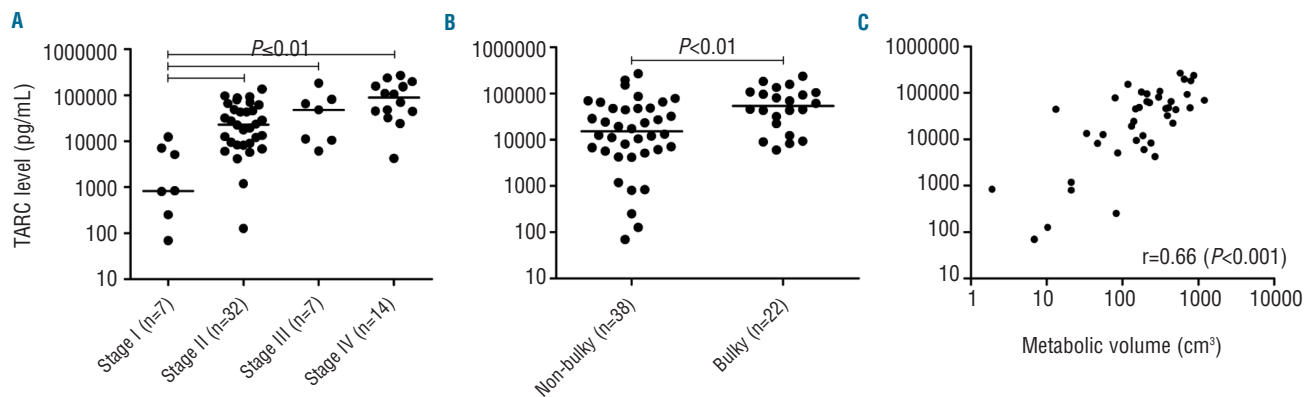


**Figure 2.** Baseline plasma TARC levels in relation to tumor burden. (A) In newly diagnosed patients, plasma TARC levels in stage II-IV disease were significantly higher compared to stage I disease ($P \leq 0.01$). (B) Patients with bulky disease had significantly higher baseline plasma TARC levels compared to patients without bulky disease ($P < 0.01$). (C) Baseline plasma TARC levels significantly correlated with the pre-treatment metabolic volume as determined by quantification of the FDG-PET results.
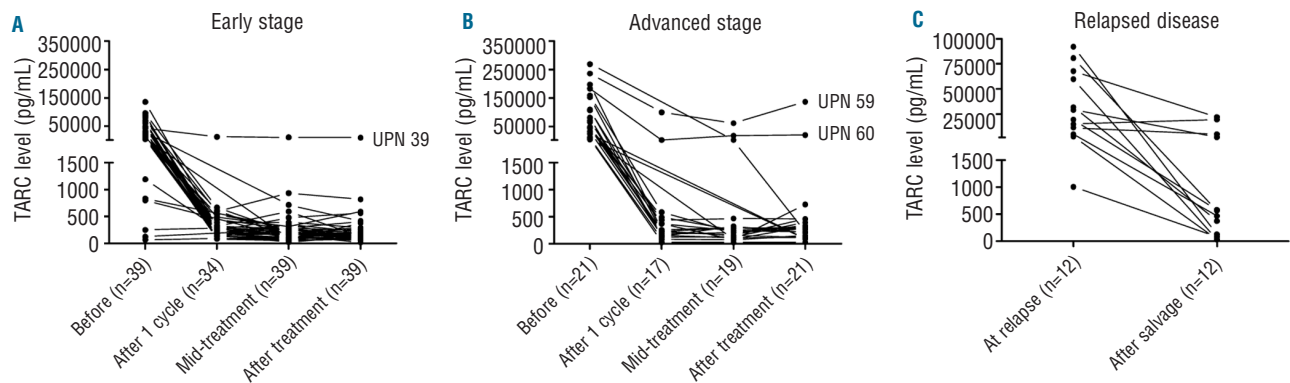


**Figure 3.** Plasma TARC dynamics in early and advanced stage newly diagnosed and relapsed cHL patients. (A) Plasma TARC dynamics before treatment, after one ABVD cycle, at mid-treatment (after 2 ABVD cycles) and after treatment among 39 newly diagnosed early stage cHL patients. All responsive patients had a decline in plasma TARC to normal range levels, while one non-responsive patient (UPN 39) had persistent high plasma TARC levels and could already be identified after one cycle of ABVD. (B) Plasma TARC dynamics before, after one ABVD or (e)BEACOPP cycle, at mid-treatment (after 4 ABVD or 4 (e)BEACOPP cycles) and after treatment among 21 newly diagnosed advanced stage cHL patients. Again, the 2 non-responsive (UPN 59 and 60) patients could be distinguished from all responsive patients already after one cycle of chemotherapy by persistent high plasma TARC levels. (C) TARC dynamics at relapse and after relapse treatment in 12 relapsed cHL patients. All 12 relapsed patients had moderate to high elevated plasma TARC levels at relapse. Four final non-responsive patients had persistent high plasma TARC levels after second-line treatment, while all responsive patients had a decline in plasma TARC to normal range levels.

a PR at mid-treatment (UPN 57). Plasma TARC was slightly elevated at mid-treatment and low at end-treatment in this patient. None of the patients with a CR relapsed (median follow up of 31 months, range 7-75).

The single patient with a final PR (UPN 58) showed low plasma TARC levels during and after treatment. After second-line chemotherapy including ASCT and IN-RT this patient remained FDG-PET positive in the same spots as observed after first-line treatment. Repeated FDG-PET studies showed that FDG uptake faded out over time and at 10 months post radiotherapy, FDG uptake disappeared.

The 2 patients with PD (UPN 59 and 60) had persistently high TARC levels during and after treatment. Both patients switched to second-line chemotherapy and one of them achieved a CR (UPN 60) with a concomitant reduction of plasma TARC to normal levels. The second patient (UPN 59) is still being treated and TARC results have to be awaited.

### Plasma TARC as a response marker in relapsed patients

All 12 patients with relapsed disease had elevated levels of TARC at relapse (Figure 3C). Eight patients achieved a CR after salvage therapy with a concomitant reduction of plasma TARC to normal range levels after treatment (Figure 3C). These 8 patients had a continuous remission (median follow up 28 months, range 3-62). Plasma TARC levels in one patient with SD (UPN 69) and 3 patients with PD (UPN 70, 71 and 72) remained elevated. Three of these patients died of lymphoma and one patient ultimately achieved a CR (UPN 71) after additional radiotherapy with concomitant normalization of plasma TARC.

## Discussion

In this study, we show that plasma TARC levels closely correlate with Hodgkin's lymphoma metabolic tumor volume, and that serial TARC levels correlate with clinical response to treatment. Interestingly, all responsive patients already had a decrease in plasma TARC after one cycle of chemotherapy while TARC levels remained high in the 3 non-responsive patients, indicating that plasma TARC might be a potential marker for very early response assessment in cHL. In addition, we show that plasma TARC is also elevated at relapse, and again correlates well with clinical response.

Since TARC is specifically produced and excreted by Hodgkin Reed-Sternberg cells, we hypothesized that plasma TARC might closely reflect cHL tumor burden. Consistent with previous studies, we showed that baseline plasma TARC levels correlate with classical clinical parameters of tumor burden, such as stage of disease and presence of bulky disease.[9,10] However, there was a considerable overlap in plasma TARC levels between the different groups defined by stage and bulk, probably because these clinical parameters are poor substitutes for total tumor load. Quantified pre-treatment FDG-PET images, reflecting metabolic tumor volume, correlated much better with plasma TARC levels. This indicates that plasma TARC levels do indeed reflect cHL tumor burden and might be an ideal marker to determine cHL disease activity.

A proportion of patients with stage I disease had low baseline plasma TARC levels, similar to those we had observed in an independent cohort in a previous study.[9] Since we now only included patients with TARC positive HRS cells, the lack of elevated plasma TARC is not caused by lack of TARC production by the tumor cells. Consistent with the correlation of plasma TARC with the metabolic tumor volume, it might be envisaged that, in some early stage cases, almost all TARC producing tumor cells are removed by the diagnostic lymph node biopsy and/or that the limited (remaining) amount of tumor cells are not capable of producing amounts of TARC that exceed the capture capacity of the surrounding or circulating CCR4+ T cells.

Early interim FDG-PET response is a predictor of final outcome in cHL.[17-24] Treatment adaptation based on the interim FDG-PET result is currently the focus of investigation in several clinical trials. Although the introduction of FDG-PET imaging has been a great breakthrough in response evaluation of malignant lymphoma, a disadvantage of using this type of imaging is the relatively high number of false positive scans during treatment.[25-31] By applying more sophisticated interpretation methods, such as the five point scale, the number of false positive scans seems to be markedly reduced compared to the dichotomous "negative or positive" evaluation that is currently used in the IHP criteria.[32-36] In contrast to FDG-PET imaging, TARC is specific for cHL tumor cell activity and seems not to be influenced by concurrent infections or inflammation caused by chemo- or radiotherapy, making plasma TARC an ideal biomarker to assess cHL treatment response.

Early plasma TARC response might be applied in the clinic to determine prognosis or to guide treatment, similar to FDG-PET imaging. In our cohort, all patients with a reduction in TARC after start of treatment had a favorable prognosis, while all patients with persistently high TARC levels failed treatment. Moreover, the 6 patients who had a PR at mid-treatment (based on FDG-PET/CT imaging) and achieved a CR at end of treatment already had low plasma TARC levels after one cycle of chemotherapy. Therefore, it is tempting to speculate that, given current FDG-PET interpretation criteria (the IHP), both positive and negative predictive value of interim plasma TARC might even be better than interim FDG-PET imaging. However, in agreement with the current favorable treatment results in cHL, our small cohort contained only 7 non-responsive patients (3 newly diagnosed and 4 relapsed). Therefore, the prognostic impact of plasma TARC could not be directly compared to interim FDG-PET images or other prognostic factors such as the IPS. Future clinical trials including both new FDG-PET interpretation criteria such as the five point scale and plasma TARC evaluation are needed to directly compare the prognostic value of these two response markers.

Our separate cohort of relapsed cHL patients showed that plasma TARC is also elevated at time of relapse, and TARC levels after salvage treatment corresponded with clinical response. Monitoring of TARC during follow up might be a minimally-invasive and effective method for evaluation of disease recurrence, potentially reducing the burden of imaging studies during follow up. Indeed, 2 relapsed patients showed elevation of plasma TARC levels months prior to actual clinical diagnosis of relapse (*data not shown*).

In conclusion, we have for the first time shown that plasma TARC levels closely reflect cHL tumor load, and

that serial plasma TARC levels correlate with treatment response. Interestingly, a change in TARC levels could already be observed after one cycle of chemotherapy, indicating its potential to serve as a very early response marker in newly diagnosed patients. However, future prospective studies should be carried out to examine the true potential of plasma TARC in response evaluation and follow up of cHL in relation to current evaluation methods.

## Authorship and Disclosures

## References

1. Kuppers R. The biology of Hodgkin's lymphoma. Nat Rev Cancer. 2009;9(1):15-27.
2. Poppema S and van den Berg A. Interaction between host T cells and Reed-Sternberg cells in Hodgkin lymphomas. Semin Cancer Biol. 2000;10(5):345-50.
3. Maggio E, van den Berg A, Diepstra A, Kluiver J, Visser L, Poppema S. Chemokines, cytokines and their receptors in Hodgkin's lymphoma cell lines and tissues. Ann Oncol. 2002;13(Suppl 1):52-6.
4. Ma Y, Visser L, Roelofsen H, de Vries M, Diepstra A, van Imhoff GW, et al. Proteomics analysis of Hodgkin lymphoma: identification of new players involved in the cross-talk between HRS cells and infiltrating lymphocytes. Blood. 2008;111(4):2339-46.
5. van den Berg A, Visser L, Poppema S. High expression of the CC chemokine TARC in Reed-Sternberg cells. A possible explanation for the characteristic T-cell infiltrate in Hodgkin's lymphoma. Am J Pathol. 1999;154 (6):1685-91.
6. Peh SC, Kim LH, Poppema S. TARC, a CC chemokine, is frequently expressed in classic Hodgkin's lymphoma but not in NLP Hodgkin's lymphoma, T-cell-rich B-cell lymphoma, and most cases of anaplastic large cell lymphoma. Am J Surg Pathol. 2001;25(7):925-9.
7. van den Berg A, Maggio E, Rust R, Kooistra K, Diepstra A, Poppema S. Clonal relation in a case of CLL, ALCL, and Hodgkin composite lymphoma. Blood. 2002;100(4):1425-9.
8. Ohshima K, Tutiya T, Yamaguchi T, Suzuki K, Suzumiya J, Kawasaki C, et al. Infiltration of Th1 and Th2 lymphocytes around Hodgkin and Reed-Sternberg (H&RS) cells in Hodgkin disease: Relation with expression of CXC and CC chemokines on H&RS cells. Int J Cancer. 2002;98(4):567-72.
9. Niens M, Visser L, Nolte IM, van der Steege G, Diepstra A, Cordano P, et al. Serum chemokine levels in Hodgkin lymphoma patients: highly increased levels of CCL17 and CCL22. Br J Haematol. 2008;140(5):527-36.
10. Weihrauch MR, Manzke O, Beyer M, Haverkamp H, Diehl V, Bohlen H, et al. Elevated serum levels of CC thymus and activation-related chemokine (TARC) in primary Hodgkin's disease: potential for a prognostic factor. Cancer Res. 2005;65(13):5516-9.
11. Kakinuma T, Nakamura K, Wakugawa M, Mitsui H, Tada Y, Saeki H, et al. Thymus and activation-regulated chemokine in atopic dermatitis: Serum thymus and activation-regulated chemokine level is closely related with disease activity. J Allergy Clin Immunol. 2001;107(3):535-41.
12. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-86.
13. Juweid ME, Stroobants S, Hoekstra OS, Mottaghy FM, Dietlein M, Guermazi A, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007;25(5):571-8.
14. Fludeoxyglucose F 18 PET Scan-Guided Therapy or Standard Therapy in Treating Patients With Previously Untreated Stage I or Stage II Hodgkin's Lymphoma. ClinicalTrials.gov. http://www.clinicaltrials.gov/ct2/show/study/NCT00433433.
15. Comparison of Two Combination Chemotherapy Regimens in Treating Patients With Stage III or Stage IV Hodgkin's Lymphoma. ClinicalTrials.gov. http://www.clinicaltrials.gov/ct2/show/NCT00049595.
16. Boellaard R, Oyen WJ, Hoekstra CJ, Hoekstra OS, Visser EP, Willemsen AT, et al. The Netherlands protocol for standardisation and quantification of FDG whole body PET studies in multi-centre trials. Eur J Nucl Med Mol Imaging. 2008;35(12):2320-33.
17. Hutchings M, Mikhaeel NG, Fields PA, Nunan T, Timothy AR. Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma. Ann Oncol. 2005;16(7):1160-8.
18. Hutchings M, Loft A, Hansen M, Pedersen LM, Buhl T, Jurlander J, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood. 2006;107(1):52-9.
19. Gallamini A, Rigacci L, Merli F, Nassi L, Bosi A, Capodanno I, et al. The predictive value of positron emission tomography scanning performed after two courses of standard therapy on treatment outcome in advanced stage Hodgkin's disease. Haematologica. 2006;91 (4):475-81.
20. Kostakoglu L, Goldsmith SJ, Leonard JP, Christos P, Furman RR, Atasever T, et al. FDG-PET after 1 cycle of therapy predicts outcome in diffuse large cell lymphoma and classic Hodgkin disease. Cancer. 2006;107 (11):2678-87.
21. Zinzani PL, Tani M, Fanti S, Alinari L, Musuraca G, Marchi E, et al. Early positron emission tomography (PET) restaging: a predictive final response in Hodgkin's disease patients. Ann Oncol. 2006;17(8):1296-300.
22. Gallamini A, Hutchings M, Rigacci L, Specht L, Merli F, Hansen M, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J Clin Oncol. 2007;20;25(24):3746-52.
23. Terasawa T, Lau J, Bardet S, Couturier O, Hotta T, Hutchings M, et al. Fluorine-18-fluorodeoxyglucose positron emission tomography for interim response assessment of advanced-stage Hodgkin's lymphoma and diffuse large B-cell lymphoma: a systematic review. J Clin Oncol. 2009;27(11):1906-14.
24. Hutchings M and Barrington SF. PET/CT for therapy response assessment in lymphoma. J Nucl Med. 2009;50:21S-30S.
25. Avigdor A, Bulvik S, Dann EJ, Levi I, Perez-Avraham G, Shemotv N, et al. Combined ESCBEACOPP-ABVD therapy for advanced Hodgkin's lymphoma patients with high IPS score: an effective regimen and low positive predictive value of early FDG-PET/CT. Haematologica. 2007;92(s5): 66.
26. Gallamini A, Viviani S, Bonfante V, Levis A. Early interim FDG-PET during intensified BEACOPP therapy shows a lower predictive value than during conventional ABVD chemotherapy. Haematologica. 2007;92 (s5):71.
27. Gallamini A, Hutchings M, Avigdor A, Polliack A. Early interim PET scan in Hodgkin lymphoma: where do we stand? Leuk Lymphoma. 2008;49(4):659-62.
28. Markova J, Kobe C, Skopalova M, Klaskova K, Dedeckova K, Plutschow A, et al. FDG-PET for assessment of early treatment response after four cycles of chemotherapy in patients with advanced-stage Hodgkin's lymphoma has a high negative predictive value. Ann Oncol. 2009;20(7):1270-4.
29. Cheson B. The case against heavy PETing. J Clin Oncol. 2009;27(11):1742-3.
30. Gallamini A. Positron emission tomography scanning: a new paradigm for the management of Hodgkin's lymphoma. Haematologica. 2010;95(7):1046-8.
31. Cheson BD. Role of functional imaging in the management of lymphoma. J Clin Oncol. 2011;29(14):1844-54.
32. Meignan M, Gallamini A, Meignan M, Gallamini A, Haioun C. Report on the First International Workshop on Interim-PET-Scan in Lymphoma. Leuk Lymphoma. 2009;50(8):1257-60.
33. Dann EJ, Bar-Shalom R, Tamir A, Epelbaum R, Avivi I, Ben Shachar M, et al. A functional dynamic scoring model to elucidate the significance of post-induction interim fluorine-18-fluorodeoxyglucose positron emission tomography findings in patients with Hodgkin's lymphoma. Haematologica. 2010; 95(7):1198-206.
34. Meignan M, Gallamini A, Haioun C, Polliack A. Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8-9 April 2010. Leuk Lymphoma. 2010;51(12):2171-80.
35. Barrington SF, Qian W, Somer EJ, Franceschetto A, Bagni B, Brun E, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. Eur J Nucl Med Mol Imaging. 2010;37(10):1824-33.
36. Meignan M. Interim PET in lymphoma: a step towards standardization. Eur J Nucl Med Mol Imaging. 2010;37(10):1821-3.