Biol Blood Marrow Transplant 20 (2014) 1982–1988

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Serum Thymus and Activation-Regulated Chemokine Level Monitoring May Predict Disease Relapse Detected by PET Scan after Reduced-Intensity Allogeneic Stem Cell Transplantation in Patients with Hodgkin Lymphoma

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Article history:
Received 16 June 2014
Accepted 19 August 2014

Key Words:
Hodgkin lymphoma
Allogeneic stem cell transplantation
Thymus and activation-regulated chemokine (TARC)

A B S T R A C T

Patients with relapsed and refractory Hodgkin lymphoma (HL) may experience long-term survival after allogeneic stem cell transplantation (alloSCT), but disease recurrence represents the main cause of treatment failure. Positron-emission tomography (PET)–positive patients after alloSCT have a dismal outcome. Serum thymus and activation-regulated chemokine (TARC) is produced by Reed-Sternberg cells and may be a marker of disease. Our study aimed at assessing whether TARC levels after alloSCT correlated with disease status and whether TARC monitoring could increase the ability to predict relapse. Twenty-four patients were evaluated in a prospective observational study. TARC serum level and PET were assessed before and after alloSCT during the follow-up (median, 30 months; range, 2 to 54). Before alloSCT, the median TARC level was 721 pg/mL (range, 209 to 1332) in PET-negative patients and 2542 pg/mL (range, 94 to 13,870) in PET-positive patients. After alloSCT, TARC was 620 pg/mL (range, 12 to 4333) in persistently PET-negative patients compared with 22,397 pg/mL (range, 602 to 106,578) in PET-positive patients ($P < .0001$). In 7 patients who relapsed after alloSCT, TARC level increased progressively even before PET became positive, with a median fold increase of 3.19 (range, 1.66 to 7.11) at relapse. The cut-off value of 1726 pg/mL had a sensitivity of 100% and a specificity of 71% for PET positivity. Patients with at least 1 TARC value above 1726 pg/mL during the first year after alloSCT had a worse progression-free survival ($P = .031$). In conclusion, TARC was correlated with disease status and its monitoring may be able to predict PET positivity after alloSCT, thus potentially allowing an early immune manipulation.

INTRODUCTION

Patients affected by Hodgkin lymphoma (HL) who are refractory or relapsed after an autologous transplantation have a very poor prognosis and short-lasting responses after chemotherapy [1,2]. Allogeneic stem cell transplantation (alloSCT) with reduced-intensity conditioning may represent a feasible option, but only 20% to 30% of allografted patients experience long-term survival; disease recurrence remains the main cause of treatment failure [3-7].

Positron-emission tomography (PET) scans have become the first-choice exam for staging and response evaluation in HL patients. In the setting of alloSCT, PET has shown to be the most sensitive exam to detect lymphoma relapse [8-10]. Patients who are or become PET-positive after an alloSCT have a very dismal outcome because of the unavailability of curative treatment options [11]. The real benefit of donor lymphocyte infusions is still unclear, as most of the responses have been achieved in combination with chemotherapy and/or after T cell–depleted transplantations [12,13]. Because immunotherapy is usually more effective when the disease is minimal, early detection of disease relapse improves the ability to cure patients [14].

The thymus and activation-regulated chemokine (TARC), also known as chemokine ligand 17, is a small cytokine belonging to the CC-motif chemokine family. TARC is expressed

Financial disclosure: See Acknowledgments on page 1987.

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http://dx.doi.org/10.1016/j.bbmt.2014.08.016
1083-8791/

constitutively by the thymus. It is produced by monocyte-derived dendritic cells and by endothelial cells and specifically binds chemokine receptor 4, which is expressed by regulatory T and T helper 2 cells. A preliminary study already demonstrated TARC expression in Reed-Sternberg cells by immunohistochemistry, thus justifying the abundant infiltrate of T helper 2 cell in the HL microenvironment [15]. The expression of TARC is particular to classic HL, as it is not expressed in lymphocyte-predominant HL and in B cell non-Hodgkin lymphomas [16]. About 85% of patients affected by HL also have elevated TARC levels in the serum at diagnosis [17,18]. Serum TARC level is correlated with disease stage, B symptoms, bulky disease and extra-nodal involvement, erythrocyte sedimentation rate, and leukocyte and lymphocyte counts [17,19]. Patients who experienced disease progression after first-line therapy had higher levels of TARC at baseline and after therapy [17,19]. In fact, a TARC level $>$ 2000 pg/mL after therapy correlated with worse survival and Sauer et al. showed that patients with a baseline TARC $>$ 10,000 pg/mL had higher risk of not responding to first-line chemotherapy [17,19]. In addition, recent data have underlined the correlation between serum TARC levels and tumor burden as detected by PET [20]. Elevated serum TARC levels have been detected in few other pathological conditions, such as atopic diseases and mycosis fungoides [21]. Based on these data, TARC may be considered a sensitive and quite specific serum marker for classical HL, although an agreement on the normal and predictive cut-off values has not yet been established [17-19,22].

Our study had the following aims: (1) to assess whether serum TARC levels correlated with disease status before and after alloSCT, (2) to correlate TARC levels with PET results after alloSCT, and (3) to evaluate whether the combined results of TARC and PET can increase the ability to assess or predict relapse after alloSCT.

PATIENTS AND METHODS

Patient Characteristics

This was a prospective observational study approved by the institutional review board. From May 2009 to March 2014, serial plasma samples were prospectively collected from 24 consecutive patients with HL who underwent an alloSCT at Fondazione IRCCS Istituto Nazionale dei Tumori. All participating patients gave their signed informed consent. Four patients who received an alloSCT during this period were not included in this analysis: 3 because of nonadherence to the protocol and 1 because of toxic death before engraftment. Table 1 summarizes patient characteristics. Patients were heavily pretreated. Twenty-three (96%) previously received an autologous transplantation. At the time of relapse before alloSCT, disease stage was distributed as follows: stage IV, n = 13 (54%; bone, n = 7; lung, n = 6; liver, n = 2; soft tissue, n = 2); stage III, n = 7 (29%); and stage II, n = 4 (17%). Three patients had B symptoms at pre-alloSCT relapse. Before alloSCT, 10 patients (42%) were in complete remission (CR), 9 (37%) were in partial remission, and 5 (21%) were in stable or progressive disease (PD/SD).

PET Monitoring

Two-deoxy-2-[fluorine-18] fluoro-D-glucose (FDG) -PET imaging was performed before alloSCT, around 1 month after alloSCT, every 3 months during the first year of follow-up, and at least every 6 months thereafter.

FDG imaging was performed 60 ± 10 minutes after intravenous injection of FDG (3 to 6 mCi/kg patient's weight), in patients in fasting status (at least 6 hours) and with blood glucose levels $<$ 140 mg/dL, using dedicated hybrid PET/computerized tomography (CT) systems (General Electric Discovery LS or 3D-TOF 64 Philips Gemini, Waukesha, WI). Imaging protocol included CT scout to define the body axial extension to be imaged (normally upper thigh to skull base), low-dose no-contrast CT scan, and PET scan. Using dedicated workstations (Philips Extended Brilliance Workspace, Eindhoven, The Netherlands), visual analysis of FDG findings was performed by 2 experienced nuclear medicine physicians, adopting the criteria suggested by Juweid et al. [23]. Briefly, an FDG-PET scan was read as positive in presence of any abnormal focal FDG uptake greater than mediastinal blood uptake, used as reference of background activity, with a corresponding morphologic alteration in the coregistered CT images. Two radiologists who had experience in lymphoma patients performed all the PET scans, and they were blinded to the fact that the patients were enrolled in the TARC study. PET scans were performed without knowledge of TARC results.

Table 1
Patient Characteristics

Characteristic	Value
No. of patients	24
Male/female, n	14/10
Age, median (range), yr	32 (18-59)
Histological subtypes, n	
Nodular sclerosis	22
Mixed cellularity	1
Lymphocyte rich	1
Time from diagnosis to alloSCT, median (range), mo	31 (16-208)
No. of previous treatments, median (range)	5 (3-12)
Previous autologous transplantations, n (%)	23 (96)
Disease stage at relapse before alloSCT, n (%)	
Stage II	4 (17)
Stage III	7 (29)
Stage IV	13 (54)
Disease status before transplantation, n (%)	
CR	10 (42)
Partial remission	9 (37)
PD/SD	5 (21)
Donor type and RIC regimen/GVHD prophylaxis, n (%)	
HLA identical sibling	
Thiothepa-fludarabine-cyclophosphamide/MTX-CSA	7 (29)
Unrelated	14 (58)
Thiothepa-fludarabine-cyclophosphamide-ATG/MTX-CSA	6
Thiothepa-cyclophosphamide-ATG/MTX-CSA	8
HLA haploidentical sibling	
Thiotepa/fludarabine/cyclophosphamide-TBI 2 Gy-+/−ATG	3 (13)

RIC indicates reduced-intensity conditioning; MTX, methotrexate; CSA, cyclosporine; ATG, antithymocyte globulin; TBI, total body irradiation.

Serum TARC Monitoring

Serum from patients was stored at −80°C until processing of samples in a double-antibody sandwich ELISA, according to the manufacturer's guidelines (R&D Systems, Minneapolis, MN). Serum TARC level was assessed in 40 healthy subjects with a similar age range as our patients and the results showed a median TARC of 325 pg/mL (range, 184 to 420). These results are in line with previous published studies and they confirm the reproducibility of the assay [17-20].

Study samples were analyzed without knowledge of disease status and treatment results. Serum TARC levels were measured before and after alloSCT. After alloSCT, TARC was measured at least every 30 days for the first 3 months; thereafter, every 2 months during the first year and then at the time of clinical check-up. In total, 222 samples were assessed after alloSCT with a median of 9 time points for each patient (range, 2 to 19). The median interval between assessments was 47 days (range, 7 to 700).

We excluded 1 patient (unique patient number [UPN] 4) from the analysis because he always presented very high TARC values regardless of disease status; therefore, we considered TARC as a nonrepresentative marker of disease in this patient.

Statistics

Continuous data differences were performed using *t*-test. To define a cut-off value of TARC with the highest sensitivity and specificity, we performed a receiver operating characteristics (ROC) curve analysis. *Progression-free survival* (PFS), defined as progression of the disease or death regardless of the cause, was estimated using the Kaplan-Meier method, and comparison of PFS between groups were performed by the log-rank test. Statistical analyses and survival curves were performed using Graphpad PRISM version 5.02.

RESULTS

Pretransplantation TARC

The pretransplantation serum TARC level was available in all but 1 patient. A pretransplantation PET was available in 14 of 22 evaluable patients. The other 8 patients were assessed

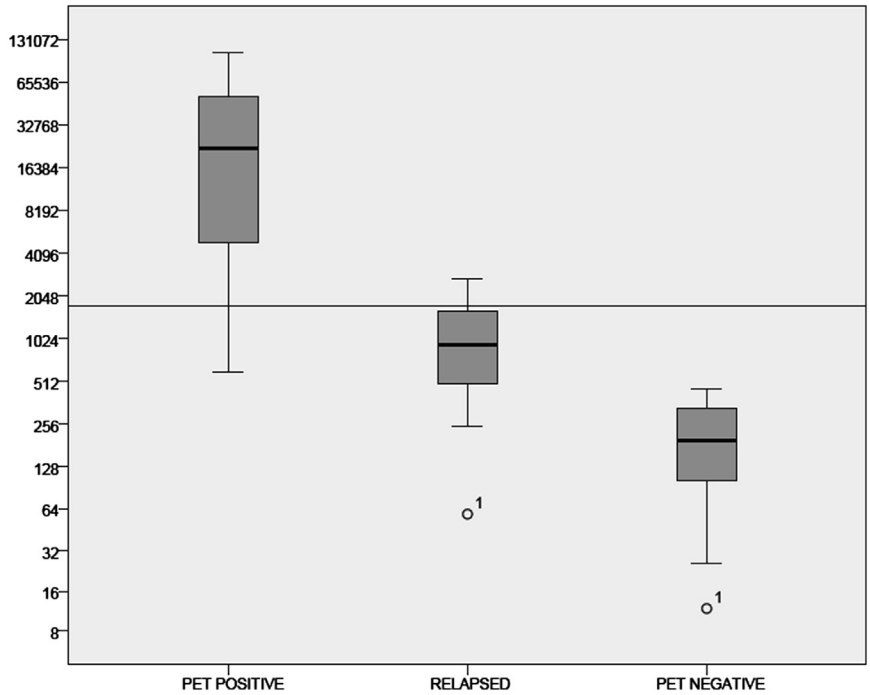

Figure 1. TARC values in PET-positive and PET-negative patients and in patients who relapsed after alloSCT. The line indicates the cut-off value of 1726 ng/mL.

by CT just before alloSCT: 4 of them because of recent radiotherapy before alloSCT and the other 4 patients because the timing of alloSCT precluded the possibility of performing the exam.

PET-positive patients had a median TARC value of 2542 pg/mL (range, 94 to 13,870), whereas PET-negative patients had a median TARC value of 721 pg/mL (range, 209 to 1332) ($P = .204$). Two patients (UPN13 and UPN18) had inconclusive PETs, due to a very low FDG uptake (standardized uptake value [SUV] ≤ 2.5) in a previously positive disease site: they had a pretransplantation serum TARC level of 710 pg/mL and 931 pg/mL, respectively.

Based on the disease status by CT or/and PET scan before alloSCT of all the evaluable 22 patients, the median serum TARC level was 684 pg/mL (range, 195 to 2293) in CR patients, 1528 pg/mL (range, 94 to 13,870) in partial remission patients, and 2516 pg/mL (range, 1159 to 5053) in PD/SD patients ($P = .108$).

Post-transplantation TARC Monitoring

The median follow-up from alloSCT was 30 months (range, 2 to 54). At the last follow-up, 2 patients died of disease progression (UPN9 and UPN14), and 2 patients died of nonrelapse mortality (UPN6 of acute graft-versus-host disease [GVHD] and UPN21 of infection).

Two patients (UPN9 and UPN14) with persistent disease after alloSCT had a median serum TARC level of 22,397 pg/mL (range, 602 to 106,578), whereas 13 patients who were in persistent CR after alloSCT had a median TARC of 620 pg/mL (range, 12 to 4333) ($P < .0001$). We excluded UPN6 because disease status was not determined at the last follow-up. Seven patients achieved PET negativity but they eventually relapsed. Their outcome has been described in detail below.

Figure 1 shows TARC values in PET-negative and PET-positive patients and in those who relapsed after alloSCT.

TARC Cut-off Value

To assess a cut-off value of TARC correlated to PET positivity, we selected only the TARC values performed on the days of PET scans (n = 66). We observed a significant difference between TARC levels correlating to a positive or a negative PET ($P < .0001$). Based on these data, the ROC curve showed that the cut-off value of 1726 pg/mL had a sensitivity and specificity of 100% and 71%, respectively.

Patients with at least 1 TARC > 1726 ng/mL during the first year after alloSCT had a 1-year PFS of 47% versus 78% of those with TARC < 1726 ng/mL ($P = .031$) (Figure 2).

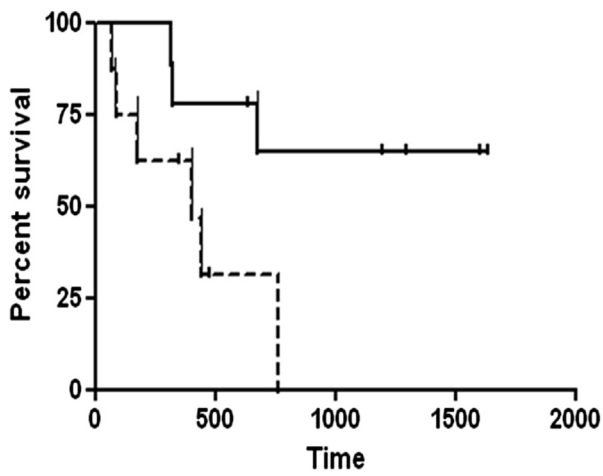

Figure 2. PFS of the patients who had at least 1 value of TARC > 1726 ng/mL within the first year after alloSCT (dotted line) and those who had always TARC < 1726 ng/mL during the first year after alloSCT (continuous line) ($P = .031$).

One-year PFS based on pre-alloSCT TARC (< versus > 1726 ng/mL) was 67% versus 53% ($P = .77$).

TARC and Relapse after alloSCT

Seven patients achieved CR after alloSCT, but they eventually relapsed after a median of 13 months (range, 6 to 25) after alloSCT. UPN1 underwent transplantation in PD with a pretransplantation TARC of 2609 pg/mL. Only 2 TARC values were available before relapse, showing a very high level 4 months before PET positivity (4108 pg/mL) and at time of relapse (3614 pg/mL). UPN2 achieved CR after alloSCT, but 9 months later, TARC started increasing above 2000 ng/mL until the end of the first year, when the TARC value reached 3506 pg/mL and the PET turned positive in a previous disease site at the mediastinum. In UPN11, TARC started increasing 5 months after alloSCT with values below 1000 ng/mL, but at that time the PET was inconclusive. He relapsed after 10 months with a TARC value of 1553 pg/mL and a positive PET at previously involved abdominal lymph nodes. UPN13 achieved PET negativity on day 30, when TARC dropped down to 361 pg/mL. From the second month, TARC increased progressively, but a CT scan on day 120 showed lymph nodes with a stable size compared with the CT scan performed before alloSCT. Six months after alloSCT, TARC was 1351 pg/mL and the PET scan showed a significant uptake in those abdominal lymph nodes. UPN15 achieved a metabolic CR on day 30 and TARC remained low during the next 15 months; then, it increased progressively achieving a value of 1558 pg/mL in the 19th month, when PET became positive as well. Similarly, UPN17 achieved PET negativity on day 60 with a TARC value of 403 pg/mL. Successively, TARC increased progressively achieving 1007 pg/mL on day 314 when the PET became positive at the lumbar spine, a previous disease site. UPN16 relapsed after 2 years: TARC value was above the cut-off of 1726 ng/mL since 1 year after alloSCT. In these 7 patients, TARC was increasing before the PET scan became positive.

Because we observed an interpatient variability of TARC values at the time of relapse detected by PET, with 4 patients relapsing when TARC was less than 1726 ng/mL, we hypothesized that the relative increase, rather than the absolute value of TARC, was suggestive of metabolic relapse. To answer this question, we compared the day-30 TARC results (when all patients had a negative PET) to the TARC value at the time of PET positivity and we observed that the median fold increase was 3.19 (range, 1.66 to 7.11). The fold increase was significantly higher compared with the fold increase of TARC of the patients who were always in CR, in which the day-30 TARC was compared with the TARC value at 1 year ($P = .038$).

Figure 3 shows the TARC monitoring in 6 patients who relapsed after alloSCT and therapy of relapse.

TARC and GVHD

Six patients (26%) experienced acute GVHD (grade 1, n = 3; grade 2, n = 2; grade 3, n = 1). Nine patients (39%) experienced chronic GVHD (limited, n = 5; extensive, n = 4).

UPN6 died of GVHD and UPN11 was still on low-dose cyclosporine therapy at the time of last follow-up because of ocular GVHD. The remaining patients experienced only transient GVHD episodes and showed no sign of active GVHD at the last follow-up.

Overall, only 7 of 222 (3%) serum TARC measures increased due to acute or chronic GVHD, whereas only 6 of them were above the cut-off of 1726 ng/mL (2.7%). UPN6 developed grade 2 acute GVHD on day 46 after alloSCT and on day 60 TARC was 4388 ng/mL, which decreased to 562 ng/mL on the next time point, when PET confirmed CR. UPN11 developed grade 2 acute GVHD on day 40 when TARC was 1734 ng/mL, but TARC decreased to 59 ng/mL 90 days later, remaining low until disease progression. UPN20 had grade 3 acute GVHD on day 30 and a serum TARC level of 4333 ng/mL that decreased to 49 pg/mL on day 60, remaining low until the last follow-up at 1 year. UPN19 had 2 elevated serum TARC levels: 1 on day 30 (2981 ng/mL) after a T cell–replete haploidentical transplantation and another on day 180 (3338 ng/mL) at the onset of eczematoid chronic GVHD. All the remaining 10 measures for this patient showed low TARC levels correlating with CR status at 15 months after alloSCT. Similarly, UPN16 had a TARC value of 2689 ng/mL on day 243 and UPN23 had a TARC value of 1690 ng/mL on day 75, when they developed a transient eczematoid form of skin GVHD.

In all of these cases, TARC was high at the time of GVHD onset and decreased rapidly over time. The pattern of increase was significantly different compared with the pattern correlated to disease relapse when TARC was persistently and/or progressively higher.

DISCUSSION

HL that relapses after an alloSCT represents an unresolved issue, as the disease is considered incurable. Recently, the results achieved with the use of new drugs, such as brentuximab, are encouraging, although they still have to demonstrate their potential in the long term [24,25]. The use of donor lymphocyte infusions alone or in combination with radio-chemotherapy or new drugs may represent an option after alloSCT, but it remains essential to detect relapse early because the graft-versus-tumor effect works when the disease is limited [14]. Unlike other hematological malignancies, in which specific tumor markers are available for minimal residual disease monitoring, PET still represents the best exam to detect disease recurrence in HL patients. Previous studies have demonstrated a sensitivity of 84% and a specificity of 90% for the detection of residual disease by PET in HL patients [26]. Despite these results, there are some open questions regarding reproducibility, mainly related to the fact that PET results are based on a visual assessment [27,28]. In our study, to increase the reproducibility of the PET results and to avoid biases, 2 experienced radiologists performed all the PET scans in HL patients and were blinded to the fact that some of them were enrolled in the TARC study. In addition, emerging data suggest that a significant portion of patients may have inconclusive or false-positive PET results, especially in some clinical conditions (eg, patients with concurrent inflammation or infection). In these cases, a disease biopsy or a second exam are recommended [29]. For all of these reasons, and taking into account that PET is a very expensive exam and exposes patients to radioactivity, the identification of a tumor marker of disease relapse would be useful.

The correlation between serum TARC with tumor burden and response after chemotherapy has already been shown. In particular, 2 recent papers correlated TARC values with PET results before and after first-line chemotherapy but, to the best of our knowledge, no data are available in the setting of alloSCT and with a longitudinal observation [19,20]. An additional marker to detect relapse, other than PET, is potentially more useful after alloSCT compared with first and second-line therapies for 2 main reasons: (1) the very high risk of relapse of allografted patients; and (2) the clinical

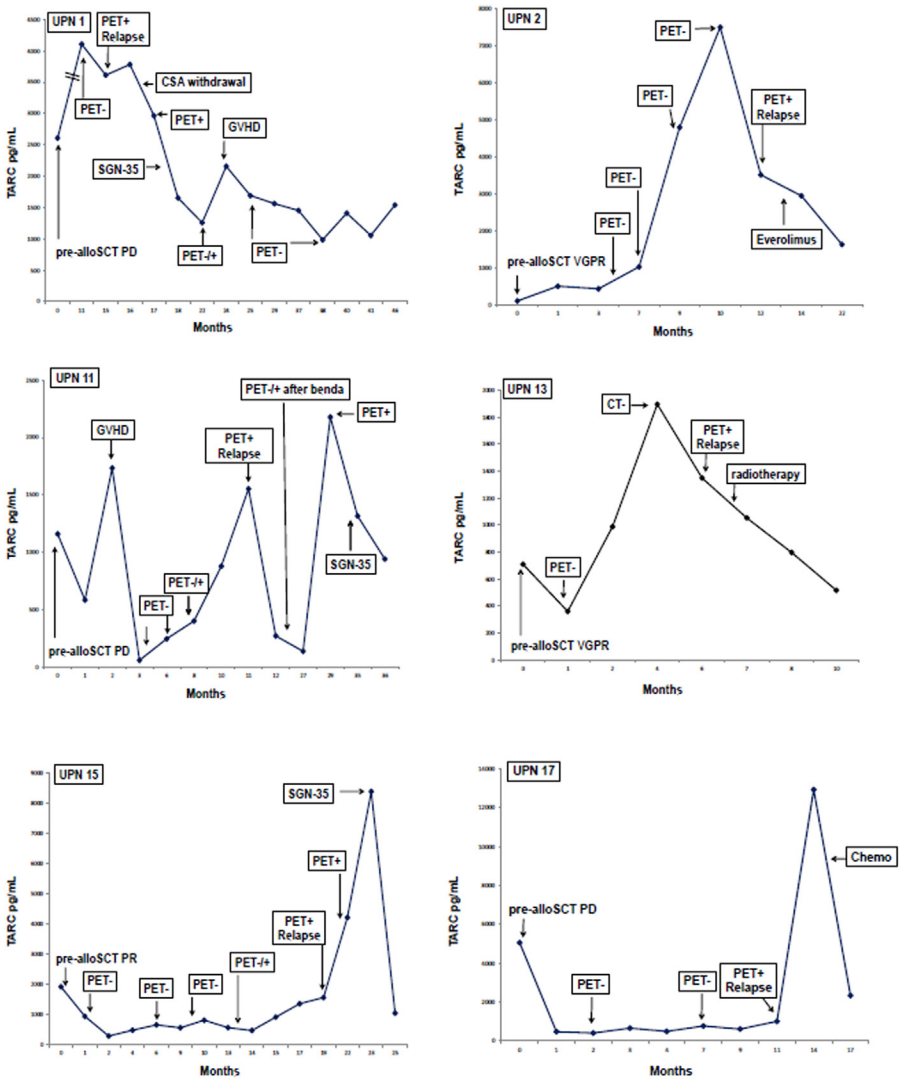

Figure 3. TARC monitoring in patients who relapsed after allogeneic stem cell transplantation. CSA indicates cyclosporine; VGPR, very good partial remission; PR, partial remission; benda, bendamustine; chemo, chemotherapy.

relevance of early detection of relapse in the context of adoptive immune therapy. As a consequence of the very small percentage of HL patients who unfortunately need an alloSCT, the number of our patients is limited compared with other studies. Nevertheless, monitoring of TARC during a median follow-up of 30 months was able to provide interesting results.

Pre-alloSCT serum TARC levels were higher in patients with active disease at the time of transplantation compared with those in CR, although the results were not significantly different, probably because of the limited number of patients. By monitoring TARC after alloSCT, we showed that those patients who were always PET-positive had significantly higher serum levels compared with those who were always PET-negative. In patients who achieved CR after alloSCT but eventually relapsed, TARC dropped down at the time of CR but then progressively increased before the PET became positive. These data suggest that TARC, which increases when the disease is still minimal and undetectable by PET, may be a very sensitive and early serum HL marker of relapse. In this regard, there are 2 limits of our study: (1) because this study started in 2009, PET results were based on Juweid criteria and not on Deauville criteria, which have been first validated to assess interim PET in HL patients undergoing first-line therapy [23,27]; and (2) we did not perform biopsies to confirm disease recurrence; however, all patients who relapsed after alloSCT were PET-positive in sites that were previously involved by lymphoma and were not easy to biopsy. We performed a ROC curve analysis by selecting those TARC values obtained at the time of PET, showing that the cut-off of 1726 pg/mL was highly sensitive and quite specific for metabolic relapse. In particular, patients who had at least 1 TARC value above 1726 ng/mL during the first year after alloSCT had a significantly worse PFS compared with those who always had a TARC less than 1726 ng/ml at 1 year after transplantation.

We identified 3 main limitations of TARC monitoring. First, TARC is not always informative, as in 1 patient TARC was always high, regardless of disease status and without any known reason. Other authors reported that TARC was not representative of disease status in about 15% of HL patients [17,18]. Thus, it is advisable to have a baseline serum TARC measure taken at diagnosis and/or at the time of high disease burden and after chemotherapy to select those patients

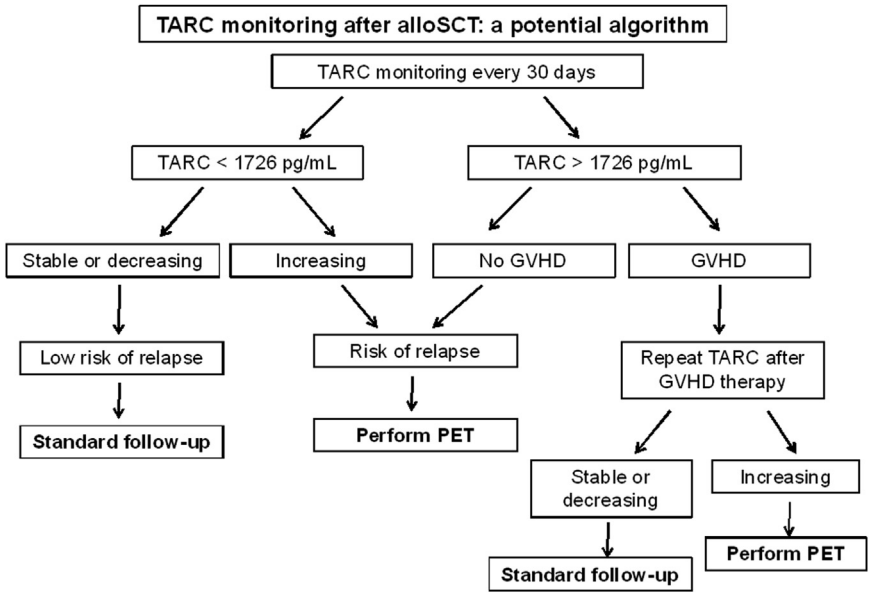

Figure 4. Potential use of TARC monitoring in patients with Hodgkin lymphoma after allogeneic stem cell transplantation.

suitable for monitoring after alloSCT. A second limit of serum TARC monitoring is related to the increase at the time of relapse. We were able to define a cut-off value of 1726 ng/mL correlating with PET positivity and this result is in line with previous published data that identified patients with TARC $>$ 2000 pg/mL as those with a decreased survival after chemotherapy [17]. Nevertheless, 4 patients relapsed with a TARC value $<$ 2000 ng/mL. Our analysis showed that the fold increase of TARC rather than the absolute value can be suggestive of relapse, underlying the importance of a sequential monitoring. A third limit of TARC monitoring is unique to the allotransplantation setting: despite the limited number of patients, we observed high serum TARC levels in some patients with GVHD, suggesting that the specificity of the marker may be low in this condition. Again, in these cases the sequential monitoring was useful as it showed a rapid decrease of TARC after initiation of therapy and/or the resolution of GVHD, instead of a progressive increase in those patients who relapsed. The increase of TARC with the onset of GVHD may be explained by previous studies carried out in atopic diseases, demonstrating the expression of TARC in the activated endothelium of inflamed skin and the stimulation of TARC production by several cytokines, such as tumor necrosis factor-α, which is also involved in the pathogenesis of the GVHD [30,31]. Notably, the small number of elevated TARC measures that was attributed to GVHD were observed in patients affected by either $\geq$ 2 grade acute GVHD or eczematoid chronic GVHD [32,33].

Taking into account these limitations, we believe that serum TARC monitoring may represent an helpful, fast, noninvasive, and low-cost tool that can be included in the post-transplantation follow-up of HL patients, together with PET, to detect disease relapse (Figure 4). Whether or not a biopsy confirmation of a PET positivity is mandatory in this setting remains open and larger prospective clinical trials are needed to address this issue and to validate our results.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

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