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Circulating biomarkers in classical Hodgkin lymphoma

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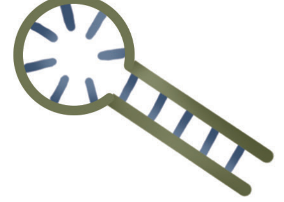

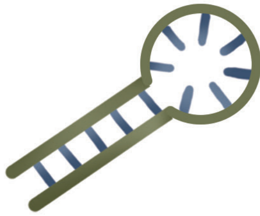

CHAPTER 8

Summary, general discussion and future perspectives

Summary and discussion

In this thesis we focused on circulating biomarkers in classical Hodgkin lymphoma (cHL). After a brief introduction on the diagnosis and treatment of Hodgkin lymphoma we discussed current knowledge on circulating biomarkers for prognostication and treatment response in ***Chapter 1***. We concluded that there is a large set of blood-based cHL biomarkers with prognostic value independent from either a set of other biomarkers or established clinical prognostic models. The reason for a lack of clinical application lies in the fact that we do not exactly know which marker or set of markers can be clinically applied together with other clinical factors as prognostic factors. This is due to lack of comprehensive studies including all relevant markers. Moreover, for most of the markers we do not know the most optimal cut-off for prognostication. To make a step forward in prognostication a new joint effort as was performed in the International prognostic factors project is necessary in which all promising biomarkers and individual clinical factors are taken into account in a homogeneously treated large study population. The most promising blood-based biomarkers that should be tested based on their consistent prognostic value in previous studies are lymphocyte/monocyte ratio, ferritin, IL6, IL10, sIL2R, IL1RA, sCD30 and TARC. The set of biomarkers that are independent from each other and from clinical prognostic factors should be included in a new prognostic model also incorporating the prognostic value of iPET. Given the fact that multiple individual factors of the IPS are outperformed by some of the above-mentioned biomarkers, we expect such a model to have improved prognostic value as compared to the IPS. Collection of plasma and serum samples upfront in clinical trials is important to facilitate joined forces on circulating biomarker-based prognostication in the future. We also concluded that research on treatment response biomarkers in cHL is more limited, but mentioned several biomarkers that have high potential to improve on or to be applied next to FDG-PET imaging.

In part 1 (Chapters 2, 3 and 4) we further investigated TARC and three other high potential circulating biomarkers for treatment response monitoring of cHL patients. In part 2 (chapters 5, 6 and 7) we investigated the role of circulating miRNAs in cHL for prognosis and treatment response monitoring.

In ***Chapter 2*** we correlated plasma TARC levels in patients with cHL with tumor burden at time of diagnosis and correlated serial plasma TARC levels during and after treatment with response to treatment. We included 107 healthy controls, 60 newly diagnosed cHL patients and 12 patients with relapsed or refractory disease. Serial TARC analyses were performed after one cycle of chemotherapy, at mid-treatment and end-treatment. We showed that mean TARC levels in cHL patients at diagnosis were approximately 400-fold elevated compared to healthy controls. Higher pre-treatment TARC levels were found in patients with more advanced disease stage. In concordance with this, we also observed a strong correlation between TARC and

metabolic tumor volume (MTV) at diagnosis. TARC levels significantly decreased in all patients upon treatment and this was already evident after one cycle of chemotherapy. Remarkably, in three non-responsive patients TARC levels remained elevated above the cut-off of 1000 pg/ml throughout treatment, whereas in all responsive patients TARC levels decreased to levels below this cut-off. In all patients with relapsed or refractory disease, TARC was elevated before start of salvage treatment and normalized after salvage treatment in responsive patients only. This study indicated that TARC is a very promising marker for prognosis and treatment response evaluation in cHL patients both at diagnosis and at relapse.

In ***Chapter 3*** we compared TARC with three other potential biomarkers for treatment response in a cohort of 103 newly diagnosed cHL patients, including the 60 patients from Chapter 2. Elevated plasma levels of sGal-1, sCD163, sCD30 and TARC were found in 67%, 21%, 91% and 93% of cHL patients, respectively. Mean plasma levels of all biomarkers decreased after treatment, but there was no correlation with change of sGal-1, sCD30, and sCD163 and clinical treatment response at an individual patient level. In contrast, TARC levels remained high in 6 out of 7 non-responsive patients and dramatically decreased in 95 out of 96 responsive patients. Jones *et al*. also analyzed sCD163 as a marker reflecting tumor micro-environment.[1] Consistent with our data, they also observed a decrease upon treatment over time. Both their and our study showed that there is considerable overlap between patients and controls and responsive and non-responsive patient making sCD163 a less attractive biomarker for treatment response. We also compared whether the method of blood collection influenced the value of the above-mentioned circulating markers in our patient cohort. Serum or platelet-rich plasma samples only differed for sCD30 levels, whereas no significant differences were observed for the other markers. In follow-up experiments not shown in this chapter, we found that TARC levels are much lower in plasma samples that are depleted of platelets. These lower TARC levels can be explained by the binding of TARC to CCR4 (the receptor for TARC), which is highly expressed on platelets.[2] In a previous study among patients with atopic dermatitis who also have elevated levels of TARC, similar results were shown when using platelet-depleted plasma instead of serum or platelet rich plasma.[3] Thus, depletion of platelets will result in lower circulating TARC levels, and as a result reduced sensitivity of TARC as biomarker for cHL. Instead, platelet rich plasma or serum are the preferred methods for TARC analysis.

To further explore the clinical usability of TARC as a treatment response marker, we compared mid-treatment or interim TARC (iTARC) with simultaneously performed interim FDG-PET (iPET) imaging in ***Chapter 4***. Interim PET is currently considered to be the gold standard for response evaluation in cHL. For this study we extended the cohort presented in Chapter 3, but focused on patients with both available TARC and PET, at diagnosis and at interim time-point, without including patients who underwent any treatment escalation based on iPET (n=95). All FDG-PET scans were reconstructed and analyzed according to the Lugano classification

including the Deauville score. Concordance between iTARC and iPET was 87%. Interim TARC was elevated in only 8% (n=9) of patients, whereas iPET was positive (Deauville ≥4) in 18% (n=17) of patients. Interim TARC positive patients finally had primary refractory or relapsed disease in eight out of nine cases, corresponding to a 5-year modified PFS rate of only 11% in the iTARC positive group. In contrast, eight out of 17 iPET positive patients had refractory disease, whereas nine had a durable remission, corresponding to a modified PFS rate of 53% in the iPET positive group. The negative predictive value was comparable with 85% for iPET and 86% for iTARC. Thus, in this study we showed that especially the positive predictive value of interim response evaluation can be increased by using iTARC instead of iPET.

Taken together, Chapters 2, 3 and 4 showed the feasibility of TARC as a biomarker for treatment response and the advantage of TARC over other circulating biomarkers. TARC is an ideal biomarker for treatment response since TARC is non-invasive and relatively easy to analyze in a reproducible manner. Additional advantages of the use of TARC over other biomarkers are the on average 400-fold elevated levels as compared to healthy controls and the fact that TARC is specifically being produced by the cHL tumor cells and thus a marker of presence of viable tumor cells (Chapter 2). *TARC* is a target gene of STAT6, which is uniformly activated in cHL by several mechanism including both exocrine and autocrine stimulation by IL-4 and IL-13 and by activation of the JAK/STAT pathway due to somatic mutations in this pathway, e.g. SOCS1 and STAT6.[4-6] This might explain why the HDAC inhibitor varinostat, an effective drug in cHL that results among others in inhibition of STAT6 phosphorylation, leads to a decrease of TARC levels.[7]

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Although TARC is secreted in high levels by HRS cells, it is also produced by dendritic cells, endothelial cells, keratinocytes and fibroblasts. Elevated levels of TARC can also be found in patients with allergic asthma and inflammatory skin diseases such as atopic dermatitis, acute and chronic urticaria and other skin diseases such as bullous pemphigoid and mycosis fungoides.[3,8-17] The common denominator of these diseases and cHL is a Th2-like environment or immune response. In general, TARC levels in these patients do not approach the levels observed in diagnostic samples of cHL patients but might interfere with TARC measurements in cHL when used for response evaluation. For example, we observed extremely high levels of TARC (163 000 pg/ml) in a cHL patient one day after a severe allergic skin reaction upon the second infusion of brentuximab-vedotin. Just before administration of brentuximab-vedotin TARC levels were within the normal range. Despite this exceptional observation, we have rarely seen discrepant levels since our introduction of TARC measurements in clinical practice for all cHL patients in the UMCG in 2014.

In recent years, TARC has gained more interest as a biomarker for treatment response mainly in ABVD-treated patients. In line with our studies Jones *et al*. showed that end-treatment TARC correlates with clinical response.[1] However, TARC levels both in patients and healthy controls in their study are different from our study, which might be explained by the use of a different

ELISA kit. Also, in line with our studies, Guidetti *et al*. showed that reduction of TARC below 800 pg/ml after the first cycle of ABVD predicted for final treatment success and PET normalization after the second cycle. TARC after one cycle was an independent predictor for PFS.[18] A more recent paper by Hsi *et al*. analyzed iTARC in an iPET-response adapted trial.[19] They showed no additional prognostic value for PFS of iTARC after 2 cycles of ABVD when treatment was intensified based on positive iPET results. It is quite possible that the limited prognostic value of elevated TARC after two cycles of ABVD in their study can be explained by the subsequent iPET-based intensification of the treatment that overruled the high risk of persistent disease reflected by elevated iTARC. To avoid this bias we only included patients who did not receive treatment intensification based on iPET for our comparison of iTARC with iPET in Chapter 4. At end-treatment, Hsi *et al*. found that elevation of TARC above the mean was predictive for both PFS and OS. This is in line with our findings that elevated TARC after treatment indeed reflects persistent disease activity.

Changes in TARC levels have also been investigated in 107 cHL patients treated with the HDAC inhibitor panobinostat. Also, in this patient group, a strong association was found between TARC reduction and clinical outcome.[20] The group of patients with TARC reductions of more than the median of the entire group at day 15 of the first course had more responders, better PFS and longer overall survival as compared to the group of patients that did not reach this TARC reduction. Feasibility of TARC as a biomarker for disease recurrence was also shown after successful treatment with allogeneic stem cell transplantation.[21] In line with this study by Farina *et al*., we have detected multiple relapses using TARC monitoring during routine follow up since clinical introduction in 2014. On the other hand, patients in persistent remission almost universally showed TARC levels <1000 pg/ml. Where serial FDG-PET images are generally considered not useful during follow-up, a simple non-invasive biomarker like TARC might be a patient-friendly method to screen for early relapse.

The studies by Harrison *et al*. and Hsi *et al*. and some other groups describe TARC after treatment as being elevated in case of a reduction less than the median levels in a group or with a cut-off defined as a percentage decrease (for example 95%) relative to baseline. However, these approaches to determine elevated TARC levels are less accurate in distinguishing normal levels as observed in healthy controls and patients in remission from pathological levels as observed in cHL patients with active disease and are thus not optimal for clinical use. For example, a 95% decrease from 200 000 pg/ml to 10 000 pg/ml will be regarded as effective response by these methods but is more likely reflecting ongoing tumor activity. On the other hand, patients with limited tumor volume at diagnosis and thus limited TARC elevation, e.g. 3 000 pg/ml will never reach a 95% reduction as the normal levels varies between 50 and 1000 pg/ml. We used normalization of TARC below a predefined cut-off of 1000 pg/ml or not. We showed feasibility of TARC normalization below a fixed threshold as a biomarker for successful treatment.

Limitations of TARC as a biomarker are that in about 10% of patients with cHL TARC levels are not elevated (i.e. below the threshold of 1000 pg/ml) at diagnosis. These cases generally involve patients with either a very low tumor volume and/or a very low percentage of HRS cells in tumor mass, resulting in circulating levels of TARC that do not exceed the cut-off (Chapter 2). In our experience, immunohistochemical staining on cHL tissue only very seldomly shows cases with TARC negative HRS cells. Second, sensitivity of TARC for detection of minimal residual disease is probably comparable to FDG-PET imaging and therefore limited since about 25% of ABVD-treated advanced stage patients relapse despite a negative interim FDG-PET.[22] Therefore, new biomarkers for minimal residual disease are still very much needed. Finally, TARC analysis is not (yet) universally available in all diagnostic laboratories making direct clinical application more difficult. Nevertheless, the commercially available ELISA kit for TARC can easily be introduced in any diagnostic laboratory.

In part 2 (chapters 5, 6 and 7) we investigated the potential value of circulating miRNAs in cHL for prognosis and treatment response monitoring. In ***Chapter 5*** we provided an overview of the knowledge on expression and function of miRNAs in cHL. Several known cancer-related miRNAs, i.e. miR-16, miR-20a, miR-21 and miR-155, were consistently reported to be abundant in cHL cell lines, isolated HRS cells and total tissue sections. Functional studies are performed for a limited number of miRNAs, but multiple target genes have been identified. Inhibition or overexpression of individual miRNAs in HL resulted in altered expression of target genes that are involved in apoptosis, proliferation, cytokine production or plasma cell differentiation. A single miRNA, i.e., miR-135a, correlated with prognosis in a single study showing the potential of miRNAs to function as biomarkers for cHL. More recently, our group confirmed the oncogenic role of miR-21 using a loss-of-function high-throughput screen and also identified three other miRNAs with oncogenic effects.[23] In addition, BTG2 and PELI1, two genes involved in regulation of apoptosis, were identified as target genes in cHL. In a second publication from our group using a small RNA sequencing approach, 84 miRNAs with differential expression in cHL cell lines compared to germinal center B-cells were identified. Inhibition of the upregulated miR-24 resulted in decreased growth at least in part caused by an increase in apoptotic cells.[24] Interestingly, several studies have shown effects of methylation of miRNA gene loci in cHL.[25-27] Navarro et al. showed that 10 miRNAs in cHL cell lines were re-expressed upon hypomethylation treatment.[27] Two tumor suppressor miRNAs, i.e. miR-34a and miR-203, were found to be methylated in cell lines and in lymph nodes of cHL patients. Hypomethylation treatment resulted in dose dependent antiproliferative effects in multiple cHL cell lines. Another study found prognostic effect of methylation of miR-124 in patient tissue samples.[25] In summary, deregulation of miRNAs is a frequent event and an important factor in the pathobiology of cHL. Future studies should further elucidate the functional effects of miRNA deregulation and clinical effect of possible miRNA inhibition in cHL patients. In chapters 6 and 7 we further investigated the potential role of circulating miRNAs as biomarkers in cHL.

In ***Chapters 6 and 7*** we described our studies on exploring the value of circulating miRNAs as biomarkers in cHL. In Chapter 6 we described the technical challenges of using circulating miRNAs as biomarkers in general. These mainly included pre-analytical challenges, such as the blood source (plasma or serum), centrifugation speed and time and types of collection tubes. Analytical factors influencing the applicability of miRNAs included RNA extraction method, amplification procedures, as well as normalization strategies and validation methods. Taking at least part of these factors into account, we aimed to identify circulating miRNAs of prognostic value in cHL patients in ***Chapter 7***. We performed a microarray-based miRNA profiling approach on RNA derived from serum samples from eight non-responsive patients and eight responsive patients from a patient cohort from Vancouver and compared their profile to each other and to eight matched healthy control serum samples. We detected expression levels above the background cutoff for 124 out of 1348 miRNAs (9%) present on the microarray. Only one of these miRNAs was significantly differentially expressed in responsive patients compared to the other two groups using multiple testing correction. However, using qRT-PCR we could not reliably detect this miRNA. We could also not detect levels above background by qRT-PCR for three out of four other miRNAs that were selected based on nominal significant differences. For the fourth miRNA we did obtain levels above background, but this miRNA was not significantly different between the groups. Of five additional miRNAs known to be highly expressed in cHL cell lines and/or tissue sections tested on the three groups, only miR-155 had significantly different levels in serum of non-responsive cHL patients compared to healthy controls, albeit with lower levels in non-responsive patients compared to healthy controls. Depletion of miRNAs from the circulation in a disease is biologically hard to explain since the majority of circulating miRNAs originates from healthy circulating cells. We concluded that we were unable to find miRNAs for which serum levels had prognostic value using a miRNA microarray profiling approach. A limitation of the direct use of plasma and serum as a source of circulating miRNAs is that there is a significant risk of admixture of miRNAs derived from PBMCs.[28]

More recently, circulating miRNAs were investigated as a biomarker in cHL by van Eijndhoven *et al.* in a small study.[29] They first isolated extracellular vesicles from plasma samples using size-exclusion chromatography. Next, small RNA sequencing was performed on RNA isolated from these vesicles. They revealed five miRNAs that were elevated in cHL patients compared to healthy controls, including two miRNAs that were also studied in our serum samples. MiRNA levels of these selected miRNAs were validated by qRT-PCR and levels decreased after successful treatment, suggesting their potential value as biomarkers for disease activity. The dynamics of miRNA levels in these patients were comparable to TARC. The main advantage of the use of extracellular vesicles as circulating miRNA source compared to plasma or serum is that it is more likely that the miRNAs identified indeed represent vital tumor activity. However, like we previously observed for sCD163, sGal-1 and

partly sCD30 there was considerable overlap between levels of the biomarker in healthy controls and cHL patients. Therefore, it is unlikely that these miRNAs will have additive value as a biomarker for cHL in a clinical setting.

Future perspectives for treatment response biomarkers in cHL

There is an urgent need to improve on current FDG-PET-based response monitoring. Currently, efforts are being made to improve interpretation and timing of FDG-PET imaging. Quantification of FDG-PET imaging focusing on alterations in standard uptake value (SUV) or metabolic tumor volume (MTV) have potential to improve interpretation and predictive value.

We are investigating very early FDG-PET-based adapted treatment in the EORTC COBRA trial for advanced stage patients (Figure 1). In this trial, FDG-PET will be performed after one cycle of brentuximab-vedotin (Br) combined with AVD chemotherapy. Based on this early FDG-PET scan patients will either continue the "less intensive" treatment with Br-ABV or switch to a more intensive scheme. We expect that very early selection of responsive patients using FDG-PET imaging will allow better selection of patients suitable for the less intensive treatment strategy without decreasing PFS. Unresponsive patients, on the other hand, will directly be switched to the more intensive treatment aiming to prevent induction of chemotherapy resistance and increase PFS.

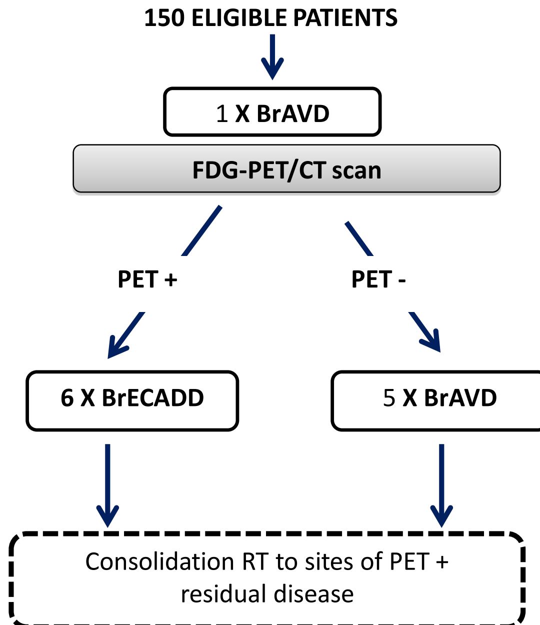

Figure 1. Design of the EORTC COBRA trial for patients with advanced stage cHL

In this trial we will also compare FDG-PET imaging with TARC analysis. Based on the results of this multicenter clinical trial and other ongoing trials investigating TARC, we expect that there will be convincing evidence that TARC can be applied in a similar way as FDG-PET imaging in the future to guide treatment based on early response. Similar to the currently running FDG-PET-response guided treatment trials, it will also be interesting to perform a TARC-response guided treatment study in the future. Normalization of TARC levels after one cycle of chemotherapy may be used as confirmation to continue the initial choice of treatment, whereas, persistence of elevated TARC might be used as a marker to switch to more intensive treatment. Current data already show that all patients with TARC <1000 pg/ml after one cycle of ABVD have a negative iPET after two cycles. Be applying TARC after one cycle of ABVD in current standard treatment, iPET can be skipped in the vast majority of patients (Figure 2). Next, implementation of TARC analysis during follow-up will enable non-invasive routine testing for disease recurrence. TARC measurements are at least as good, much more patient-friendly and much cheaper than FDG-PET imaging. The latter point being especially relevant in this era of rising health care costs and for countries where FDG-PET is not universally available.

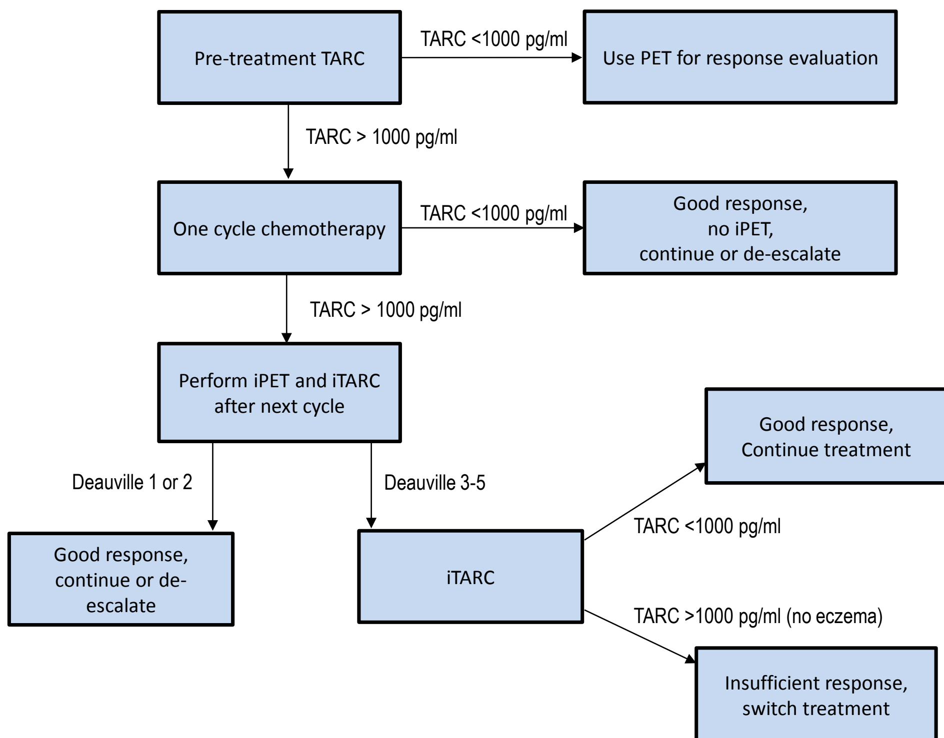

Figure 2. Possible clinical application of TARC in cHL response evaluation

To improve on the negative predictive value of iTARC and iPET, there is still a need for new biomarkers that can detect minimal residual disease (MRD). Recently, it was shown that genomic aberrations, including copy number alterations and mutations, can be detected in plasma of patients with cHL using next generation sequencing.[30] Decreased circulating tumor DNA (ctDNA) levels correlated with successful treatment whereas less than 2 log decrease of ctDNA levels correlated with disease relapse, despite negative interim FDG-PET. Analysis of ctDNA is therefore a very interesting potential method to detect MRD, and might also provide information on the biology of disease and possible clonal evolution. Similar to studying other circulating markers, blood collection procedures also play a crucial role in effectiveness of ctDNA analysis as a tool to monitor MRD. In addition, the applied NGS approach including read depth and the use of unique molecular indexes to discriminate between unique molecules, needs to be considered to achieve high sensitivity. At the moment NGS-based approaches require up to 60 ml of blood to obtain sufficient levels of ctDNA to allow reliable detection of somatic aberrations as a measure for MRD. In addition to NGS-based approaches, follow-up of driver mutations using ultra-sensitive methods such as digital droplet PCR has a high potential of being more sensitive in detecting MRD compared to FDG-PET imaging and TARC analysis.

With all new promising techniques mentioned above, more insight will be obtained in the pathobiology of cHL, resulting in better response monitoring and tailored treatment approaches, ultimately resulting in better survival and quality of life after treatment for cHL patients.

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TARC