Early-mid treatment C-reactive protein level is a prognostic factor in aggressive non-Hodgkin’s lymphoma

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Abstract

Background: In the light of an emerging role for early-mid treatment 18 F-deoxyfluoroglucose positron emission tomography (FDG-PET) as an important prognostic indicator in aggressive non-Hodgkin’s lymphoma (NHL), we attempted to determine whether a simple parameter, such as the early-mid treatment CRP (C-reactive protein) level, could also be utilized as a significant prognostic factor in aggressive NHL. Patients and methods: Serum CRP levels were monitored in 55 patients with aggressive NHL. The lowest value of the early mid-term CRP levels recorded was compared with the interim PET-CT results, as well as with the clinical course and eventual outcome. Results: During chemotherapy, the lowest value of early-mid treatment CRP levels significantly predicted the results of the interim FDG-PET (P = 0.04 with an odds ratio of 1.13). Patients who did not achieve an early-mid treatment CRP level of <5 mg/L, had a shorter time to disease progression or relapse (P = 0.001) as well as a reduced overall survival (OS) (P = 0.016). Conclusions: The early-mid treatment serum CRP level is a prognostic factor in aggressive NHL. Patients who do not achieve an early-mid treatment level of <5 mg/L have quicker disease progression or earlier relapse and also appear to have an inferior OS.

Key words C-reactive protein; early-mid treatment; prognostic factor; aggressive non-Hodgkins lymphoma

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In order to improve the therapeutic approach in aggressive non-Hodgkin’s lymphomas (NHL) many clinical and biological prognostic factors have been suggested. The majority of the prognostic factors are determined at diagnosis or at the time of relapse and the International Prognostic Index (IPI) (1) is currently used as the standard risk stratification. In recent years, early response to treatment has also been shown to be an important prognostic factor (2–9). Patients who do not achieve complete remission (CR) after 1–3 cycles of chemotherapy are regarded as high risk for end treatment failure, relapse and shorter survival (2–9). Early detection of these poor responders helps to make timely changes in the therapeutic approach.

During the last two decades, a few reports have suggested that pretreatment serum CRP levels could be used as a simple and valuable prognostic factor in NHL (10–12). Serum CRP levels are higher in NHL patients compared with the levels evident in healthy individuals (11) and the concentration of CRP appears to correlate with the histological subtype (11). Higher pretreatment CRP levels are also associated with B-symptoms (10), more advanced stage (11) and shorter overall survival (OS) (10). At the end of treatment, in most patients who achieve CR, the CRP levels return to the normal range (12). In lymphomas, the high serum CRP levels reflect the elevated serum inflammatory cytokines levels that are associated with the malignant process and in particularly of Interlukin-6 (IL-6). IL-6 is a major inducer of CRP synthesis in the liver and in NHL it is produced and secreted also by the lymphoma cells (13–15). The
malignant cells are probably a major source of the circulating IL-6 (14, 15) and the secreted II-6 can further enhance the proliferation of the tumor cells (15).

In the present study, we report for the first time that the early-mid treatment CRP level is a prognostic factor in aggressive NHL. The early-mid treatment CRP levels appear to correlate with the interim positron emission tomography-computed tomography (PET-CT) findings and with the overall clinical outcome.

**Patients and methods**

We collected available clinical data on 55 patients with untreated and relapsed aggressive NHL seen at the Tel-Aviv Sourasky Medical Center between 2004 and 2006. The characteristics of the patients are shown in Table 1. All biochemistry results taken routinely before each chemotherapy cycle were recorded. Wide range CRP was analyzed by an immunoturbidimetric assay on the ADVIA 1650 chemistry system (Bayer, Leverkusen, Germany) using Bayer ADVIA kit for CRP. The lowest value of CRP and lactate dehydrogenase (LDH) recorded at the first day of the second, third or fourth cycle of chemotherapy was defined as the early-mid treatment CRP/LDH (in all patients the recorded CRP values were drawn when no active infectious complications were evident and the patients were eligible for chemotherapy treatment). The early-mid treatment CRP and LDH levels were compared with the interim PET-CT results, as well as with the clinical course and outcome. Serum CRP levels at the range of 0–5 mg/L were considered as normal. Progression-free survival (PFS) was defined as the time from diagnosis (first diagnosis or first time of relapse) until evidence of disease progression or subsequent relapse after CR. Overall survival was defined as the time from diagnosis until death from any cause. The study was approved by the local institutional review board.

**Statistics**

The results of the numerical variables are expressed using their medians and the Inter Quartile Range (IQR) displayed as the 25th and the 75th percentiles, the results of the categorical variables are expressed using their frequencies and percentages. Since wide-ranged CRP is not normally distributed, its natural log transformation was used. All continuous variables were compared between the groups using the non-parametric Mann–Whitney test. The chi-squared test and the fisher exact test were used to examine the association between categorical variables. Kaplan–Meier analysis was used in order to examine the PFS and OS curves and log rank test to compare between the subgroups. Multivariate analysis was performed by using Cox regression method. P-value ≤ 0.05 was considered as statistically significant. The statistical analysis was performed using the SPSS software, version 13.0 (SPSS, Chicago, IL, USA).

**Results**

**Baseline CRP**

Prior to the first cycle of chemotherapy the median [IQR] CRP level was 33.3 [9.4–99.2] mg/L (Table 2). Patients with aggressive NHL presenting with B-symptoms or bulky disease (tumor diameter >10 cm) had higher pretreatment CRP levels compared to those recorded in asymptomatic patients and those without bulky disease (median [IQR] 102.0 [11.6–148.3] mg/L vs. 29.9 [6.2–45.0] mg/L, P = 0.02 and median [IQR] 64.7 [29.9–124.0] mg/L vs. 17.1 [6.2–42.1] mg/L, P = 0.01, respectively). Pretreatment CRP levels were also significantly higher in more advanced disease stages (stage II, III, IV) when compared to localized disease, stage I (median [IQR] 35.4 [11.5–101.2] mg/L vs. 6.2 [1.7–32.1] mg/L, P = 0.023). No significant correlations were found between pretreatment CRP levels and IPI or extranodal involvement (P = 0.25 and 0.70, respectively).
Early-mid treatment CRP predicts outcome in aggressive NHL

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Table 2 Medians [IQR] of Baseline CRP levels and early-mid treatment CRP levels according to the patients’ different categories

<table>
<thead>
<tr>
<th>Histology</th>
<th>Baseline CRP</th>
<th>Early-mid CRP</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large cell</td>
<td>34.9 (11.7–100)</td>
<td>2.4 (0.7–8.2)</td>
<td>&lt;0.001</td>
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<tr>
<td>Follicular grade 3</td>
<td>9.2 (4.2–15.1)</td>
<td>1.8 (0.3–5)</td>
<td>0.028</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>36.2 (1.6–44.6)</td>
<td>3.8 (0.2–7.4)</td>
<td>0.109</td>
</tr>
<tr>
<td>Peripheral T-cell</td>
<td>99.2 (20.4–147)</td>
<td>5.8 (2.2–24)</td>
<td>0.018</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>6.2 (1.7–32.1)</td>
<td>0.9 (0.2–8.1)</td>
<td>0.028</td>
</tr>
<tr>
<td>Stage II–IV</td>
<td>35.4 (11.5–101.2)</td>
<td>3.6 (1.0–7.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bulky disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Bulky</td>
<td>17.1 (6.2–42.1)</td>
<td>3.1 (0.4–7.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bulky</td>
<td>64.7 (29.9–124)</td>
<td>2.4 (1.4–6.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>B-symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-Symptoms</td>
<td>29.9 (6.2–45)</td>
<td>3.1 (0.6–8.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>B-Symptoms</td>
<td>102 (11.6–148.3)</td>
<td>2.6 (0.8–6.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>IPI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/low-intermediate risk</td>
<td>28 (6.2–58.8)</td>
<td>2.8 (0.3–7.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High-intermediate/high risk</td>
<td>35.4 (13.6–103.6)</td>
<td>2.8 (0.9–9.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein.

With a median follow-up of 363 days (range 82–726) of this study, pretreatment CRP levels ≥20 mg/L were associated with a trend for shorter PFS compared to lower CRP levels but it did not reach statistical significance (P = 0.06). On the other hand, patients with baseline CRP levels ≥20 mg/L had an inferior OS compared to those with CRP levels < 20 mg/L (P = 0.029). In multivariate Cox regression analysis including baseline CRP levels, age, B-symptoms, LDH, stage, bulky disease, extra-nodal involvement and IPI, the association between IPI and OS was the only significant factor (P = 0.05).

**Early-mid treatment CRP**

During chemotherapy, the median [IQR] lowest early-mid treatment achieved was 2.8 [0.8–7.6] mg/L (Table 2). The early-mid treatment CRP significantly correlated with the results of the interim FDG-PET (P = 0.04, odd ratio of 1.13, 95% CI: 1.01–1.27). In this logistic model, a calculated threshold of 50% was determined to differentiate between high or low probability for having positive interim FDG-PET with a positive predictive value (PPV) of 75% and a negative predictive value (NPV) of 70%. Correlating early-mid treatment CRP levels to FDG-PET findings of minimal residual F-18 FDG uptake (defined as reduction of ≥90% in the pathological F-18 FDG volume) improved substantially the PPV and the NPV to 87.5%. Early-mid treatment CRP levels also correlated with a reduction of 50% or more in the lymph nodes diameter as recorded in the mid-term CT scan.

(P = 0.02 with a odds ratio of 1.21, 95% CI: 1.03–1.44), while it had a PPV of 100% and a NPV of 87%.

Patients who did not achieve an early-mid treatment CRP level of < 5 mg/L, had a shorter time to disease progression or relapse compared to those who achieved CRP levels of below this cut-off level (P = 0.001, the median PFS in the high CRP subgroup was 12 months, while it was not reached in the lower CRP subgroup), [Fig. 1A]. Patients with an early-mid treatment CRP level above 5 mg/L also had a reduced OS compared with those who reached lower CRP levels (P = 0.016, median OS was not reached in both subgroup), [Fig. 1B]. The combined analysis of the early-mid treatment CRP levels and the interim FDG-PET findings correlated better with time to progression or relapse compared with interim FDG-PET only (P = 0.005). However, this binary analysis did not demonstrate a better correlation with OS compared to the interim FDG-PET alone (P = 0.08).

In multivariate Cox regression analysis including age, B-symptoms, pretreatment CRP and LDH levels, stage, bulky disease, extra-nodal involvement, IPI, early-mid LDH, early-mid CRP and interim FDG-PET, only stage, early-mid treatment CRP levels and interim FDG-PET results significantly correlated with PFS (P = 0.029, 0.02, and 0.004, respectively). However, the early-mid treatment CRP levels and IPI significantly correlated with OS (P = 0.016 and 0.03, respectively).

**Discussion**

In the present study, we report for the first time that the early-mid treatment CRP level is a valuable prognostic factor in aggressive NHL. Patients who do not achieve an early-mid treatment CRP below 5 mg/L have a
shorter time to disease progression or relapse and an inferior OS.

Early-mid treatment CRP also significantly correlated with the interim FDG-PET findings having a PPV of 75% and NPV of 70% when strictly applying the definition of a negative FDG-PET as no evidence of any pathological 18F-FDG uptake in primary involved sites. However, when using a more liberal, but less objective definition of minimal residual 18F-FDG uptake (a reduction of ≥90% in the pathological 18F-FDG volume or intensity) (6, 9, 16), the PPV and NPV of early-mid treatment CRP levels improved substantially to 87.5%. Furthermore, the combined analysis of the early-mid CRP and the interim FDG-PET results seemed to correlate better with time to disease progression or relapse compared to using the interim FDG-PET alone. Based on these results, it seems that monitoring serum CRP levels before each cycle of the chemotherapy in patients with aggressive NHL may be useful for clinical follow-up. Those patients who have persistent high serum CRP levels during the first few cycles of the treatment should be carefully evaluated for a possible poor response. On the other hand, patients with persistent high CRP levels but who responded well to the therapy should be watched closely for an early relapse.

Our results also indicate, that baseline CRP levels are higher in patients with B-symptoms, bulky disease, and who have more advanced disease stages. Similarly, other earlier studies in NHL have also shown that baseline serum CRP levels are higher in patients with more aggressive histology (11, 17) (also in our unreported data) and in patients who present with B-symptoms (10, 17), bulky disease or advanced stage (11, 12, 17). Although higher baseline serum CRP levels correlate with poorer parameters of the disease, it appears based on a multivariate analysis that the early-mid treatment CRP correlates better with PFS and OS than baseline CRP values and even better than serum LDH levels.

The significance of CRP as a prognostic factor in NHL actually reflects the high serum inflammatory cytokines levels and particularly of Interlukin-6 (IL-6), associated with the malignancy. In another study, similarly to our results, Pederson et al. (18) showed that serial serum IL-6 measurements may serve an early indicator of response to treatment in aggressive NHL, while a significant decrease of serum IL-6 early after the first cycle of chemotherapy correlated with the achievement of a complete remission at the end of the treatment and with borderline significance for the prediction of survival (18).

Obviously there are some limitations for using CRP levels as a prognostic factor in NHL. CRP is a non-specific acute phase reactant, and therefore its predictive value as a single measurement cannot be relied upon and serial measurements should be performed. Furthermore, we observed that during therapy, and for a few days following discontinuation of granulocyte colony-stimulating factor (GCSF), serum CRP levels increased, and therefore, careful interpretation of these levels is warranted in patients who have received GCSF just before serum levels of CRP are measured. In this regard, an elevation of various cytokines including IL-6, IL-1β, and TNF-α has been reported during GCSF treatment (19) and we assume that the release of these cytokines plays a major role in the elevation of CRP during GCSF treatment.

In conclusion, in this study, we have shown that the early-mid treatment CRP levels may serve as a reliable prognostic factor in patients with aggressive NHL. Because of the fact that CRP is a simple and routinely available laboratory test, it can easily be utilized in this clinical setting. Currently, we suggest that persistent high CRP levels during the first few cycles of chemotherapy should be regarded as an alert for possible treatment failure in patients with aggressive NHL. Large prospective studies will be needed in the future before employing CRP in other clinical decision strategies.

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References


