



Revista Brasileira de Hematologia e Hemoterapia Brazilian Journal of Hematology and Hemotherapy

www.rbhh.org



Original article

Evaluation correlates C-reactive protein with advanced stage Hodgkin's lymphoma and response to treatment in a tertiary university hospital in Brazil



Talita Máira Bueno da Silveira da Rocha*, Ana Luiza Pereira Miranda Silva, Sérgio Costa Fortier, Carlos Sérgio Chiattonne

Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP), São Paulo, SP, Brazil

ARTICLE INFO

Article history:

Received 14 November 2014

Accepted 27 April 2015

Available online 3 June 2015

Keywords:

Hodgkin disease

C-reactive protein

Prognosis

ABSTRACT

Objective: To demonstrate a correlation of C-reactive protein levels with disease stage and response to treatment in Hodgkin's lymphoma patients of the Hematology Service of Santa Casa de São Paulo.

Methods: A retrospective study based on review of medical records was carried out of 38 patients diagnosed with Hodgkin's lymphoma between October 2010 and December 2012. Three patients met the exclusion criteria, giving a final sample of 35 patients for analysis. C-reactive protein levels >1 mg/dL were considered positive.

Results: Among the patients analyzed, median age was 29 years, 65% were male and 85% had the classical nodular sclerosis subtype. Twenty-nine (82%) were in the advanced stage and 28% had bulky mass at diagnosis. Seventeen percent had bone marrow invasion by lymphoma. Baseline C-reactive protein levels were associated with both stage (p -value = 0.0035) and presence or absence of B symptoms (p -value = 0.008). The highest C-reactive protein levels were detected in patients with advanced disease while no patients with localized disease had C-reactive protein >5 mg/dL (p -value = 0.02). After the first treatment cycle, C-reactive protein fell to near-normal levels and no direct association with response pattern was found. As the mean follow-up was only 14 months, it was not possible to determine whether relapse was accompanied by a further increase in C-reactive protein.

Conclusion: Baseline C-reactive protein levels directly correlated with stage and presence or absence of B symptoms, but the degree of improvement with treatment did not correlate with response pattern. After a longer follow-up, it may be possible to assess whether relapse correlates with a further increase in C-reactive protein levels.

© 2015 Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. Published by Elsevier Editora Ltda. All rights reserved.

* Corresponding author at: Rua Alameda Joaquim Eugênio de Lima, 712, apt° 1111, Jardim Paulista, 01403-000 São Paulo, SP, Brazil.

E-mail address: tasilveira6@yahoo.com.br (T.M.B. da Silveira da Rocha).

<http://dx.doi.org/10.1016/j.bjhh.2015.05.003>

1516-8484/© 2015 Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. Published by Elsevier Editora Ltda. All rights reserved.

Introduction

Hodgkin's lymphoma (HL) is a localized or disseminated malignant lymphoproliferative disease which primarily involves the lymph nodes, spleen, liver and bone marrow.

The estimated prevalence of HL for 2014 in the United States is 9190 new cases, accounting for 11.5% of all lymphomas and 0.55% of all cancers diagnosed.¹ The incidence rate is 1.3–1.4:100,000.²

Discovered in 1930 by Tillet and Francis, C-reactive protein (CRP), as well as the erythrocyte sedimentation rate (ESR) a well established inflammatory marker used in a large number of prognostic indicators for lymphoma, is an acute-phase protein induced by pro-inflammatory cytokines, in particular interleukin 6 (IL-6), but also interleukin 1 (IL-1) and tumor necrosis factor-alpha (TNF- α), and synthesized by hepatocytes. CRP is a nonspecific marker of inflammation. Generally, an elevation in CRP occurs 4–6 h after the onset of inflammation, production doubles by eight hours and peaks at 36–50 h. CRP levels remain elevated during the inflammation process and drop sharply upon resolution.³

In addition, CRP has been used as a diagnostic and prognostic marker for a number of neoplasms, particularly colon, ovarian and breast cancer as well as hepatocellular carcinoma and other malignant diseases. A correlation between interleukin 2 and CRP has been found in various neoplasms.^{4–6}

In lymphomas, elevated CRP levels reflect the increase in inflammatory cytokines, particularly IL-6, which are associated with malignant processes. IL-6 induces the production of CRP by the liver and in HL patients, and this cytokine is produced by the cells of the lymphoma.⁷

In 1978, CRP was described as a biochemical marker of HL in adults.^{8,9} Another study in 1985 showed elevated CRP in patients with advanced HL.¹⁰

Objective

The objective of this study was to demonstrate the correlation between CRP levels and disease stage and response to treatment of HL patients.

Methods

Patients diagnosed with HL and treated in the Outpatient Clinic of the Hematology Service of Santa Casa de São Paulo between October 2010 and December 2012 were assessed.

The exclusion criteria were incomplete data in medical records, and first line treatment without response data at time of analysis.

A retrospective analysis of clinical and laboratory data was carried out by a single observer based on medical records. The following data were collected: age at diagnosis, gender, presence of bulky mass at diagnosis, disease stage (I and IIB without bulky mass was defined as initial stage and IIB with bulky mass, III and IV as advanced stage), CRP at diagnosis and after each cycle of chemotherapy, type of treatment (chemotherapy, radiotherapy) mid-treatment response (early), response at end of treatment, and relapse.

In addition, possible adverse factors associated with elevated CRP levels were assessed, such as infection during treatment and the use of granulocyte-colony stimulating factor (G-CSF).

Response to treatment was assessed using the Cheson criteria.¹¹ No patient in this sample had been submitted to positron emission tomography (PET).

The exams determining CRP levels were performed by the central laboratory of the Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP) one week before the first cycle of chemotherapy as part of the initial assessment of the patient and repeatedly throughout treatment (one week before each cycle of chemotherapy). CRP levels >1 mg/dL were considered elevated. The CRP exam was performed by the particle-enhanced immunoturbidimetric assay technique. CRP agglutinates with latex particles coated with anti-CRP monoclonal anti-bodies and the precipitate is determined turbidimetrically.

Statistical analysis was performed using Pearson's Chi-square test and Student's t-test. A p -value ≤ 0.05 was considered statistically significant. Data processing and statistical analyses were carried out using the statistical software package SPSS version 15.0 for Windows.

Results

Of the 38 patients diagnosed with HL, three patients were excluded due to missing data, giving a total of 35 patients for analysis.

The median age was 29 years, 65% were male, 85.7% had classical HL with the nodular sclerosis subtype and 11.5% had the mixed cellularity subtype. Eighty-two percent of patients were at an advanced stage and 28% had a bulky mass at diagnosis. In addition, 17% had bone marrow invasion by the lymphoma (Table 1). Median follow-up was 14 months.

Table 1 – Epidemiologic clinical data of patients.

Characteristic	Number (n = 35)
Age – years (median)	29 years
Gender – n (%)	
Male	22 (65)
Female	13 (35)
CRP – n (%)	
<1 mg/dL	10 (28.5)
>1 mg/dL	25 (71.5)
Disease – n (%)	
Localized	6 (18)
Advanced	29 (82)
B symptoms – n (%)	
Present	23 (68)
Absent	12 (31)
Subtype – n (%)	
Nodular sclerosis	30 (85.7)
Mixed cellularity	4 (11.5)
Rich in lymphocytes	1 (2.8)
Nodular lymphocyte-predominant	1 (2.8)

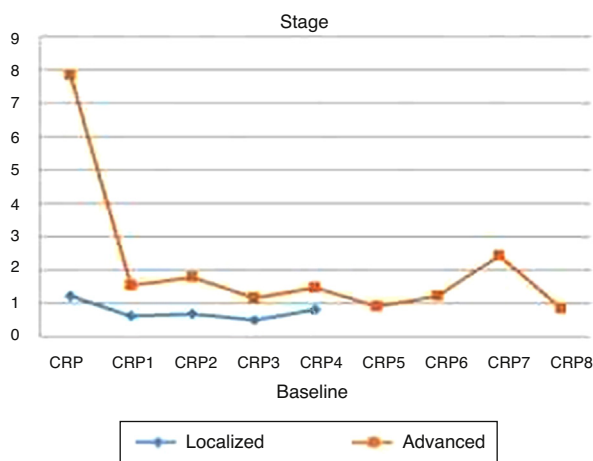


Figure 1 – Median C-reactive protein (CRP; mg/dL) at baseline and after each cycle according to stage.

An assessment of the baseline CRP showed that the levels were significantly associated with disease stage. Mean CRP in patients in the advanced stage of the disease was 7.85 ± 7.7 mg/dL whereas mean CRP in those with localized disease was 1.21 ± 1.6 mg/dL (p -value = 0.0035). An analysis was performed using a cut-off for CRP of 5 mg/dL. Under these conditions, 50% of patients with advanced disease and no cases with localized disease had CRP exceeding this level (p -value = 0.02) (Figure 1).

On assessing the association between baseline CRP levels and presence of B symptoms, the mean CRP in patients without B symptoms was 2.18 ± 3.63 mg/dL versus 8.395 ± 7.97 mg/dL in patients presenting with B symptoms (p -value = 0.008) (Figure 2). After the first treatment cycle, the association between CRP levels and patients with or without B symptoms was no longer statistically significant (1.435 mg/dL versus 0.957 mg/dL; p -value = 0.412).

Assessment of the relationship between baseline CRP and initial response revealed a mean baseline CRP of 5.2 ± 7.63 mg/dL in patients attaining full response (FR) at mid-treatment and a mean of 7.6 ± 7.57 mg/dL in those attaining a partial response (PR). However, these results were not statistically significant (p -value = 0.42). Using the cut-off of 5 mg/dL for baseline CRP, 33% of patients attaining FR and

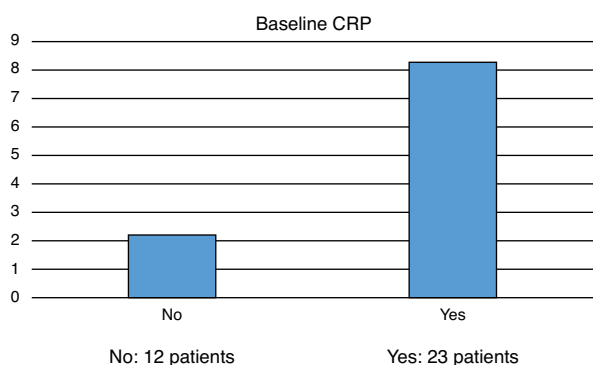


Figure 2 – B Symptoms and baseline C-reactive protein level (CRP; mg/dL).

42% attaining PR had a baseline CRP ≥ 5 mg/dL, again without statistical significance (p -value = 0.46).

Assessment of response at end of treatment and CRP levels at baseline revealed a mean of 5.69 ± 7.89 mg/dL in the group attaining FR and 5.82 ± 7.22 mg/dL in the group attaining PR (p -value = 0.49).

Considering the cut-off point of ≥ 5 mg/dL and final response, 27% of patients with FR and 55% of those with PR had CRP ≥ 5 mg/dL (p -value = 0.16).

Thus, over half of the patients with PR at the end of treatment had baseline CRP ≥ 5 mg/dL versus only 27% of those attaining FR even though this was not statistically significant.

Analysis of CRP levels after the first chemotherapy cycle (CRP1) identified no statistically significant association with stage, initial response or final response.

With regard to stage, mean CRP1 was 1.52 ± 1.82 mg/dL for cases with advanced disease and 0.61 ± 0.30 mg/dL in those with localized disease (p -value = 0.245).

In relation to early response, the mean CRP1 of patients attaining FR was 1.14 ± 1.56 mg/dL versus 1.37 ± 1.78 mg/dL for those with PR (p -value = 0.75).

On analyzing the final response, the mean CRP1 was 0.98 ± 1.31 mg/dL for the group attaining FR versus 2.3 ± 2.42 mg/dL for the group attaining PR (p -value = 0.127).

Discussion

The characteristics of the patient sample of the present study were similar to those reported in the literature; the median age was 29 years, and they were predominantly male and with the nodular sclerosis histological subtype. In contrast with the international literature, the majority of our patients were diagnosed in an advanced stage (82%). This may be explained by difficulties accessing the Brazilian National Health Service (SUS) and the slowness of the series of exams and procedures the patient must undergo to reach the definitive diagnosis of the neoplasm.

In the current study, an association was identified between baseline CRP and the presence of B symptoms, with higher baseline CRP levels in patients with B symptoms than those without B symptoms (8.395 mg/dL \times 2.18 mg/dL; p -value = 0.008). This relationship was also found by Wieland et al.¹² in their study analyzing CRP in 95 children with HL, for which the mean CRP level in patients with B symptoms was 8.0 mg/dL compared to 1.3 mg/dL (p -value < 0.001) in subjects without B symptoms.

In addition, Zielinski et al.¹⁰ analyzed the acute-phase proteins CRP, alpha 1-antitrypsin and alpha 1-glycoprotein acid in 15 patients with advanced HL and found that all patients with B symptoms at diagnosis also had higher CRP levels than subjects without B symptoms (p -value < 0.02). This correlation was also found in the current study.

One explanation for these findings is that B symptoms, particularly fever, reflect greater tumor inflammatory activity.

In the present retrospective cohort, a relationship between baseline CRP and disease stage was established. The highest CRP levels were detected in those with advanced disease (mean baseline CRP: 7.85 ± 7.7 mg/dL; p -value = 0.0035) (Figure 2). Also, when the cut-off point of 5 mg/dL was used,

none of the patients with early stage disease had CRP levels above cut-off whereas half the patients in an advanced stage had CRP levels exceeding this value (p -value = 0.02). Similar findings were found by Child et al.⁹ in a vertical study in which 31% of patients with localized and 53% with advanced disease exhibited high levels of this protein.

Zielinski et al.¹⁰ analyzed 15 patients with advanced HL and found elevated baseline CRP levels in all patients (mean baseline CRP: 18.8 ± 5.8 mg/dL) and a significant decline in levels after commencing treatment (p -value < 0.001). This latter finding was also observed in the present analysis where, irrespective of stage, initial response or final response, the level of CRP fell sharply after commencing treatment.

In the present study, although a relationship between baseline CRP level and disease stage was initially established, CRP returned to normal or near-normal levels in all patients following the first cycle of chemotherapy. This most likely occurred owing to a reduction in tumor inflammatory activity, but it had no direct correlation with the disappearance or otherwise of the neoplasm. None of the patients with localized disease had baseline CRP levels exceeding 5 mg/dL and only 50% of patients with advanced disease had CRP over 5 mg/dL. Moreover, in the present study, eight patients (three with advanced and five with localized disease) had low baseline CRP levels, six of which were below the detectable level. Of these six patients, three had advanced disease. This most probably compromised the response assessment.

In this study, a sharp fall in CRP to levels under 2 mg/dL was observed within three chemotherapy cycles. Only one refractory patient failed to attain this level. The CRP concentration in this patient fell to 3 mg/dL and then rose to over 5 mg/dL without further decrease. Therefore, CRP may be analyzed as a prognostic marker where treatment failure or the need for therapeutic change is indicated when levels do not fall shortly after starting therapy.

In the analysis of the present cohort, the assessment of baseline CRP and initial and final response to treatment, although not reaching statistical significance, showed that patients who attained initial and final PR had the highest mean CRP levels at baseline, whereas those who attained FR had the lowest mean levels. The baseline CRP level therefore may serve as a predictor of treatment response. Patients with highest baseline CRP levels most likely have a more advanced stage of disease. This relationship was shown by the present investigation and likewise by other studies.^{9,10} Thus, patients with higher baseline CRP are likely to have a poorer response to treatment. Further comparative studies are needed to confirm this theory.

There are several limitations to using CRP as a prognostic factor in HL. CRP is an acute-phase protein and therefore the predictive value of a single measurement should not be considered in isolation but used in the context of a series of measurements. This is true because other situations can also lead to elevated CRP levels. One such situation is the use of G-CSF during treatment, which leads to an increase in the CRP protein both during and several days after discontinuing use of the factor. This occurs because the medication leads to an increase in the number of cytokines such as IL-6, IL-1 and TNF- α .¹³ CRP may also increase during infection. Therefore, a multivariate analysis should be performed in an effort

to understand these confounding factors. This analysis was not carried out in the present study and therefore it should be seen as a limitation.

Our case series has several other limitations, such as the small number of patients, the retrospective nature of the analysis, and the large percentage of patients with advanced disease and with B symptoms.

Even though this retrospective analysis did not show statistical significance between CRP levels and the initial and final responses obtained with treatment, it appears to be a promising prognostic marker. Given that the study had an average follow-up of only 14 months, it was not possible to assess CRP as a predictor of relapse. Further studies with longer follow-ups are therefore required to verify this hypothesis. In addition, a study involving multivariate analysis and comparing CRP levels using PET is warranted in a bid to identify CRP as a potential predictor of relapse and as a prognostic marker.

Conclusion

An association was found between elevated CRP levels and both advanced disease and the presence of B symptoms in this study. CRP was not a predictor of response or relapse.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer Statistics, 2014. *CA Cancer J Clin.* 2014;64(1):9–29.
2. Macmahon B. Epidemiological evidence of the nature of Hodgkin's disease. *Cancer.* 1957;10(5):1045–54.
3. Mahmoud FA, Rivera NI. The role of C-reactive protein as a prognostic indicator in advanced cancer. *Curr Oncol Rep.* 2002;4(3):250–5.
4. Legouffe E, Rodriguez C, Picot MC, Richard B, Klein B, Rossi JF, et al. C-reactive protein serum is a valuable and simple prognostic marker in non Hodgkin's lymphoma. *Leuk Lymphoma.* 1998;31(3-4):351–7.
5. Kodama J, Miyagi Y, Seki N, Tokumo K, Yoshinouchi M, Kobashi Y, et al. Serum C-reactive protein as a prognostic factor in patients with epithelial ovarian cancer. *Eur J Obstet Gynecol Reprod Biol.* 1999;82(1):107–10.
6. Nozoe T, Matsumata T, Kitamura M, Sugimachi K. Significance of preoperative elevation of serum C-reactive protein as an indicator for prognosis in colorectal cancer. *Am J Surg.* 1998;176(4):335–8.
7. Specht L. Prognostic factors in Hodgkin's disease. *Semin Radiat Oncol.* 1996;6(3):146–61.
8. Child JA, Cooper EH, Illingworth S, Worthy TS. Biochemical markers in Hodgkin's disease and non-Hodgkin's lymphoma. *Recent Results Cancer Res.* 1978;64:180–9.
9. Child JA, Spati B, Illingworth S, Barnard D, Corbett S, Simmons AV, et al. Serum beta 2 microglobulin and C-reactive protein in the monitoring of lymphomas: findings in a multicenter study and experience in selected patients. *Cancer.* 1980;45(2):318–26.
10. Zielinski CC, Preis P, Aiginger P, Eibl MM. Acute-phase-proteins and parameters of humoral immunity

- in patients with advanced Hodgkin's disease. *J Cancer Res Clin Oncol.* 1985;110(1):65-70.
11. 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.
 12. Wieland A, Kerbl R, Berghold A, Schwinger W, Mann G, Urban C. C-reactive protein (crp) as tumor marker in pediatric and adolescent patients with hodgkin disease. *Med Pediatr Oncol.* 2003;41(1):21-5.
 13. Herishanu Y, Perry C, Braunstein R, Metser U, Goor O, Rogowski O, et al. Early-mid treatment C-reactive protein level is a prognostic factor in aggressive non-Hodgkin's lymphoma. *Eur J Haematol.* 2007;79(2):150-4.