C-Reactive Protein Level: A Key Predictive Marker of Cachexia in Lymphoma and Myeloma Patients

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Abstract

Background: Cachexia is defined as an involuntary loss of weight, characterized by a loss of skeletal muscle mass with or without fat mass loss. It increases mortality risk and decreases quality of life in patients with lymphoma or myeloma. Early markers of cachexia are not identified. The objective of this work was to identify risk factor of cachexia in a cohort of patients with hematological malignancies to develop strategies to prevent cachexia and its consequences.

Methods: Clinical and biological parameters were collected before and at the end of the treatment. Quantification of weight loss during cachexia was performed by the method of Martin. Clinical responses to treatment of patients with lymphoma or myeloma were monitored.

Results: Thirty-eight percent of the 145 patients enrolled were cachectic at the end of treatment. Classical prognostic disease scores at the time of diagnosis seemed to be not associated with cachexia observed at the end of treatment. Only C-reactive protein (CRP) > 54 mg/L seemed to be a risk factor of cachexia (P = 0.023, odds ratio (OR): 5.94 (1.55 - 39.14), confidence interval (CI): 1.55 - 39.14). Those results were confirmed by bootstrap analysis.

Conclusion: This study highlights that high CRP level at diagnosis seems to be a risk factor for cachexia during treatment, permitting to identify patients at risk and in future to implement preventive strategies.

Keywords: Cachexia; Lymphoma; Myeloma; CRP; Inflammation

Introduction

Cachexia is defined by an involuntary weight loss that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment [1]. Weight loss in cancer cachexia can be classified according to Martin et al score [2]. Cachexia is characterized by muscle mass loss with or without fat loss [1] and can be explained by complex phenomena like a decrease in protein synthesis promoting depletion of muscle tissue [1, 3] and an increase in inflammation level [3]. This inflammation is a key marker of cachexia and is characterized by an increase in biochemical markers such as C-reactive protein (CRP), inflammation marker secreted by the liver in response to increase in interleukin-6 (IL-6) level [1, 4, 5]. During hematological malignancies, cachexia concerns more than 30% of patients, with an increase of mortality risk and a decrease of quality of life [6]. The role of chemotherapy in this cachexia either by improving cancer-related cachexia or by inducing cachexia itself is well recognized [1]. Despite identification of mechanisms leading to a loss of muscle mass, the precise identification of cachexia risk factors before cancer treatment remains insufficient and their influence on patient outcome is not defined. Thus, the objective of this work was to identify risk factors of cachexia in myeloma and lymphoma patients, from the outset of cancer diagnosis, to develop strategies to prevent cachexia and its consequences.

Materials and Methods

Patients

This study was based on a prospective and observational study (NCT02134574). One hundred forty-five patients diagnosed with lymphoma or myeloma (aged > 18 years) between 2014 and 2017 were enrolled and completed their treatment. This cohort consisted of a prospective collection of clinical and biological data, from patients consulting for a diagnosis of hematological malignancies within the Department of Clinical Hematology of the Montpellier University Hospital. Clinical responses to treatment of patients were monitored according to international recommendations using prognostic indicators [7, 8] and the disease relapse date was identified to determine progression-free

survival (PFS). This study was approved by the Institutional Ethics Committee in accordance with the principles of the Helsinki Declaration (National Agency for the Safety of Medicines and Health Products (ANSM), reference: ANSM 13029B-11 of 21/03/2013, Committee for the Protection of Persons (CPP) Sud mediterranee I, reference: 13 24 of 02/04/2013).

Cachexia diagnosis

Each patient losing weight during treatment was considered cachectic, including cachexia induced by treatment. Cachexia was determined at the end of the hematological treatment. For that, a severity stage between 0 and 4 was attributed according to Martin criteria [2] (where stage 0 is the lowest severity stage and stage 4 is the highest severity stage of cachexia).

Statistical analysis

Distributions of data were tested with the Shapiro-Wilk test. Chi-squared or Fisher's exact tests were used to compare categorical data. For numerical data, medians were compared using Student's t-test or Mann-Whitney's test. Spearman's correlation test was used to assess the association between two numerical variables. The association between covariates and cachexia was assessed using multivariate logistic regression analysis. The receiver operating characteristics (ROC) curve was used to determine the threshold value to predict cachexia associated with the best sensitivity and specificity according to the Youden index [9]. Results from Cox regression was internally validated using bootstrap procedure [10, 11], generating a total of 1,000 replicates. PFS was measured from the date of the initiation of treatment to the date of relapse and/or progression. PFS was estimated using the Kaplan-Meier method and comparisons were made using the log-rank test. Hazard ratios (HRs) and their 95% confidence intervals (CIs) in univariate and multivariate analyses were calculated using Cox regression analyses. All statistical analyses were performed at the conventional two-tailed α level of 0.05 using R software version 3.0.2.10.

Results

Patients

Of the 145 patients, 89 were men and 56 were women. Thirty of patients were diagnosed for Hodgkin's lymphoma, 84 patients for non-Hodgkin's lymphoma and 31 for myeloma. All clinical and biological data are shown in Table 1.

Cachexia prevalence

The average time interval between the two weight measurements was 8 months (i.e. treatment time). Fifty-five out of 145 patients (38%) present a cachectic state at the end of treatment (Fig. 1): 11 with a weight loss of severity 0 (7.5% of 145 pa-

tients), 17 with a severity 1 (12%), 11 with a severity 2 (7.5%), 13 with a severity 3 (9%) and three with a severity 4 (2%).

Risk factors for cachexia and patients' outcome

Classic disease prognostic scores were not significantly associated with cachexia (Table 2). Among the biological and clinical data, only CRP seems to be associated with cachexia. The ROC curves were used to determine a threshold value of 54.0 mg/L for CRP level at diagnosis that discriminated between patients who were cachectic or not cachectic during treatment. A CRP level greater than 54.0 mg/L at diagnosis appears to be a risk factor for cachexia during treatment ($P = 0.023$, odds ratio (OR): 5.94, CI: 1.55 - 39.14). These results were confirmed by bootstrap analyse, and a CRP > 54 mg/L still appears to be a risk factor for cachexia (OR: 8.17, CI: 3.44 - 19.41) (Table 2). Nine patients died as a result of treatment and 34 relapsed (median: 26.3 months; min.: 7.3; max.: 45.0; interquartile range (IQR): 18.5 - 33.2). At diagnosis, CRP > 54 mg/L appears to be a risk factor for relapse ($P = 0.012$, HR: 2.96, CI: 1.22 - 7.14), as well as Ann Arbor stage ($P = 0.033$, HR: 0.32, IQR: 0.11 - 0.96).

Discussion

CRP level at diagnosis: a risk factor for cachexia at the end of treatment of lymphoma or myeloma

High CRP level at cancer diagnosis appears to be a cachexia risk factor for 38% of patients losing weight during hematological treatment. These results are consistent with our bootstrap analysis, but had never been highlighted in hematology. Indeed, the increase in inflammation level, symbolized by an increase in CRP level, is one of the major mechanisms of cachexia that can lead to loss of muscle mass and increase mortality risk [1, 12].

CRP level at diagnosis: a risk factor for relapse of lymphoma or myeloma

In addition, high CRP level at diagnosis appears to be a risk factor for relapse and therefore a risk factor for early mortality. This relationship could reflect a cachexia not previously diagnosed or sarcopenia (i.e. muscle deconditioning linked to advanced age [13]). Indeed, inflammation could reflect sarcopenia development [14] instead of cancer-related cachexia, seeing that the median age of the patients in the present study is 62 years. Finally, a high level of inflammation could also reflect advanced stages in cancer at diagnosis [15]. These data can enable clinicians to identify patients at risk for cachexia and implement preventive strategies to reduce its prevalence.

Limitations

This study presents different limitations or bias. Cachexia was only assessed at the end of treatment. We have no follow-up

Table 1. Clinical and Biological Data at Diagnosis

|	Cachexia cohort (n = 145)		
	n (%)	Median (IQR)	Range
Age at diagnosis (years)	-	62.4 (48.0 - 70.9)	20.0 - 90.6
Male sex	89 (61)	-	
Weigh at diagnosis (kg)	-	71.0 (60.0 - 82.0)	40.7 - 116.8
Height (cm)	-	170.0 (164.0 - 176.0)	145.0 - 197.0
BMI at diagnosis	-	24.3 (21.5 - 27.6)	16.2 - 39.4
Tobacco status			
Never smoked	66 (45.5)	-	
Old smoker	55 (38)	-	
Actual smoker	24 (16.5)	-	
Hemoglobin (g/L)	143 (99)	13.0 (11.5 - 14.1)	7.5 - 17.4
Total proteins (g/L)	122 (84)	71.5 (68.0 - 76.0)	38.0 - 106.0
Albumin (g/L)	122 (84)	40.2 (36.1 - 42.9)	17.1 - 48.6
CRP (mg/L)	114 (79)	5.0 (2.1 - 18.4)	0.3 - 245.7
Creatinine (µmol/L)	141 (97)	73.0 (60.0 - 86.0)	44.0 - 256.0
CKD-EPI (mL/min/1.73 m^2)	140 (97)		
< 60	19 (14)	-	
> 120	16 (11)	-	
60 - 120	100 (71)	62.4 (48.9 - 70.9)	20.0-90.6
Pathology			
HL	28 (19)	-	
NHL	86 (59)	-	
Myeloma	31 (22)	-	
Lymphoma			
Ann Arbor stage* I-II	37/97	-	
FLIPI < 2	8/13	-	
MIPI < 3	3/6	-	
IPI < 3	18/29	-	
Myeloma			
ISS index I	16/25	-	
PCLI (%)	24	0.23 (0.10 - 0.61)	
Ratio tumoral/normal plasmocytes	27	22.8 (6.4 - 49.0)	

*For all lymphomas. BMI: body mass index; CKD-EPI: chronic kidney disease epidemiology collaboration; CRP: C-reactive protein; FLIPI: follicular lymphoma international prognostic index; HL: Hodgkin lymphoma; IPI: international prognostic index for other lymphoma; IQR: interquartile range; ISS: international scoring system for multiple myeloma; NHL: non-Hodgkin lymphoma; MIPI: mantle cell international prognostic index; PCLI: plasma cell labeling index.

of the evolution of patients' weight loss during treatment. Furthermore, we used only weight loss to diagnose cachexia, which can be insufficient [16]. Computed tomography scan or magnetic resonance imaging could be used due to their higher precision about body composition.

Perspectives

In our study, 38% of patients are cachectic during treatment for a lymphoma or a myeloma. Beyond the probable changes in quality of life, we suggest also that these patients can present an increased risk of mortality [2, 17]. With the identification of high CRP level as a diagnostic cachexia risk factor and a relapse risk factor, the implementation of preventive strategies is possible, favorable and recommended [12]. Indeed, cachexia is a phenomenon that is not completely reversible, whose main mechanisms are an increase in the level of inflammation and a negative imbalance in protein synthesis [1]. The practice of physical activity, and particularly adapted physical activity,
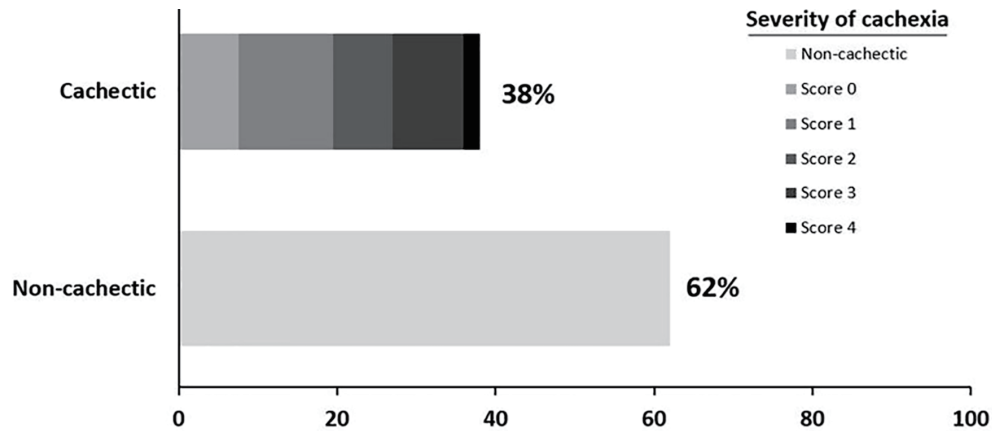
Figure 1. Proportion (%) of the cachectic (n = 55) and the non-cachectic (n = 90) patients. Cachexia prevalence is represented by the score of weight loss severity (score of Martin): weight loss of severity 0 (n = 11), severity 1 (n = 17), severity 2 (n = 11), severity 3 (n = 13) and severity 4 (n = 3).

Table 2. Association Between Parameters Measured at Diagnosis and Cachexia During Treatment

	Original data		Bootstrap analysis (1,000 replicates)
	OR (95% CI)	P	Mean OR (95% CI)
Total proteins > 72.5 g/L, n = 54/122	1.62 (0.77 - 3.47)	0.208	1.48 (1.38 - 1.58)
Albumin > 41.3 g/L, n = 43/122	1.21 (0.56 - 2.65)	0.635	1.39 (1.29 - 1.49)
CRP > 54.0 mg/L, n = 16/114	5.94 (1.55 - 39.14)	0.023	8.17 (3.44 - 19.41)
Hemoglobin > 12.0 g/L, n = 90/143	1.39 (0.69 - 2.79)	0.353	1.14 (1.03 - 1.27)
Creatinine > 93.5 μmol/L, n = 26/141	0.30 (0.12 - 0.73)	0.009	0.78 (0.64 - 0.96)
Pathology			
HL, n = 30	Ref		NA
NHL, n = 84	0.45 (0.17 - 1.16)	0.098	NA
Myeloma, n = 31	0.37 (0.12 - 1.11)	0.077	NA
Treatment per pathology			
HL, n = 30	Ref		NA
DLBCL, n = 35	0.36 (0.12 - 1.06)	0.063	NA
Other lymphoma, n = 49	0.52 (0.19 - 1.46)	0.217	NA
Myeloma, n = 31	0.34 (0.12 - 1.11)	0.077	NA
Lymphoma			
Ann Arbor stage* I-II, n = 37/97	1.15 (0.49 - 2.73)	0.752	1.37 (1.26 - 1.49)
FLIPI < 2, n = 8/13	0.36 (0.01 - 10.68)	0.509	NA
MIPI < 3, n = 3/6	6.29×10^8 (0 - NA)	0.997	NA
IPI < 3, n = 18/29	0.38 (0.08 - 1.65)	0.202	0.74 (0.52 - 1.06)
Myeloma			
ISS index I, n = 16/25	2.89 (0.24 - 67.90)	0.414	NA
PCLI < 0.63 (%), n = 18/24	0.20 (0.01 - 1.58)	0.142	NA
Ratio tumoral/normal plasmocytes < 8.15 , n = 9/27	0.51 (0.09 - 2.57)	0.350	0.76 (0.47 - 1.24)

*For all lymphomas. CI: confidence interval; CRP: C-reactive protein; DLBCL: diffuse large B-cell lymphoma; FLIPI: follicular lymphoma international prognostic index; IPI: international prognostic index for other lymphoma; ISS: international scoring system for multiple myeloma; HL: Hodgkin lymphoma; MIPI: mantle cell international prognostic index; NHL: non-Hodgkin lymphoma; OR: odds ratio; PCLI: plasma cell labeling index.

would be one of the ways to prevent its appearance and is part of the management recommendations [12, 18, 19].

Conclusion

This study has highlighted that high CRP level at diagnosis seems to be a risk factor for cachexia during treatment and a risk factor for relapse.

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None.

Financial Disclosure

Conflict of Interest

All authors declare that they have no conflict of interest.

Informed Consent

Each patient provided a written informed consent.

Author Contributions

Joris Mallard, Anne Laure Gagez and Guillaume Cartron have written the article. Guillaume Cartron worked on the study design and Pierre Louis Bernard, Aline Herbinet, Jonathan Maury and Cedric Baudinet read and approuve the final manuscript, and help for the results analysis. All authors accepted the final version of the manuscript.

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