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Chapter

5

Prognostic significance of geriatric assessment in combination with laboratory parameters in elderly patients with aggressive non-Hodgkin lymphoma

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Abstract

The age-adjusted International Prognostic Index (IPI) is an important prognostic factor for patients with non-Hodgkin lymphoma (NHL). We investigated whether a geriatric assessment (GA) is of additional prognostic value in NHL. In this prospective cohort study of 44 patients aged 70 years or older with NHL receiving R-CHOP, a GA was administrated before the start of chemotherapy. GA was composed of Mini Nutritional Assessment (MNA), Groningen Frailty Indicator (GFI), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Mini Mental State Examination (MMSE) and levels of albumin, creatinine, lactate-dehydrogenase (LDH) and hemoglobin. Multivariate analyses were performed using logistic regression and the cox regression model. After adjustment for sex, age, comorbidity and univariate laboratory values with $p \leq 0.1$, abnormal MNA and GFI scores and low hemoglobin level were associated with not being able to complete the intended chemotherapy: odds ratio (OR) 8.29 (95% confidence interval [CI]: 1.24-55.6; p = 0.03), 9.17 (95% CI: 1.51-55.8; p = 0.02) and 5.41 (95% CI: 0.99-29.8; p = 0.05), respectively. Adjusted for sex, age, comorbidity, age-adjusted IPI and univariate laboratory values with $p \leq 0.1$, frailty by GFI and low hemoglobin were associated with worse survival with hazard ratio (HR) of mortality of 2.55 (95% CI: 1.07-6.10; p = 0.04) and 4.90 (95% CI: 1.76-13.7; p = 0.002), respectively. We conclude that (risk of) malnutrition, measured with the MNA, frailty, measured with the GFI, and low hemoglobin level had additional predictive value for early treatment withdrawal, and GFI and hemoglobin were, independent of the age-adjusted IPI, predictive for an increased mortality risk.

Introduction

Non-Hodgkin lymphomas (NHL) form the largest group of malignancies (40-50%) within the range of hemato-oncological diseases [1, 2]. The median ages of diagnosis and death are 66 and 75 years, respectively [3, 4]. Aggressive B-cell NHL is the most common lymphoid tissue neoplasm in adults and occurs frequently in elderly patients [5]. The incidence steadily increases with age [6].

Since the 1970s the first generation chemotherapy regimen with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) remains the best available treatment after comparison with second generation regimens, as was shown in a randomized trial of patients with advanced stage aggressive B-cell NHL [7]. Rituximab has been added to the standard treatment since more than ten years (R-CHOP) [8]. In patients over 80 years old a reduced dose of CHOP with rituximab (R-miniCHOP) has been suggested as new standard treatment [9].

The process of aging is associated with increasing functional impairment and increasing comorbidity [10] and age is a well-established prognostic factor for NHL. In 1993, the International NHL Prognostic Factors Project developed the International Prognostic Index (IPI) with the risk factors age, stage, performance status, lactate dehydrogenase (LDH) and extranodal sites of disease. The age-adjusted IPI, originally developed for patients of 60 years and younger but also shown to be applicable for older age groups, is defined by the risk factors stage, performance status and LDH [11].

A comprehensive geriatric assessment (GA) can be a useful tool in the management and follow-up of elderly patients [12-14]. A comprehensive GA provides information on the functional status of older cancer patients with the combined objective and subjective information on comorbidity, functional-, nutritional-, and psychosocial status. Several studies have been published underscoring the usefulness of some form of GA [9, 15-18]. Application of GA in a cohort of 143 patients with NHL demonstrated the importance of instrumental activity of daily living (IADL) score and comorbidity as prognostic variables for survival [18]. The R-miniCHOP study showed that a decreased serum albumin was an important risk factor for survival [9] and this was also found in a study among NHL patients over 90 years of age [19]. In a cohort of 348 elderly patients, among whom 105 patients with non-Hodgkin lymphoma, male sex, advanced stage, poor MNA score and a prolonged timed get up and go (GUG) test were associated with a higher risk of mortality [16]. Tailored treatment based on GA identified three groups in a study of 91 elderly patients with diffuse large B-cell lymphoma (DLBCL): fit patients, patients with comorbidity, and frail patients. The overall survival of fit patients was significant better in comparison with the other two groups [17]. Finally, in a study of 100 elderly NHL patients, three subgroups could be characterized by GA: fit, unfit and frail. They received R-CHOP mitigated in dose and drugs according to co-morbidity, activities of daily living (ADL) and IADL scores, resulting in manageable toxicity and excellent outcome [15].

The aim of the present prospective study is to investigate the prognostic value of GA in addition to the age-adjusted IPI for patients aged 70 years and older diagnosed with non-Hodgkin lymphoma and treated with R-CHOP.

Patients and Methods

Study design

This prospective cohort study involved patients aged 70 years or older (n = 90) with non-Hodgkin lymphoma who were considered fit to be treated with chemotherapy by their hematologist. Patients were recruited between May 2004 and February 2010 from three general and one university hospital. To investigate a homogeneous patient population we selected all patients with DLBCL and follicular lymphoma grade III who were treated with R-CHOP (n = 44). The excluded 46 patients (of whom 12 patients with DLBCL) who were treated with other schemes than the R-CHOP regimen were comparable for the following baseline characteristics compared to the included patients: male gender (53% vs 43%; P = 0.39), age (mean = 77 yr vs 78 yr, P = 0.48), Karnofsky Index (median = 0, vs median = 0; p = 0.56), age-adjusted IPI of 2 to 3 (55% vs 46%; p = 0.47) and 2 or more comorbidities (53% vs 46%; p = 0.82), see figure 1. We included follicular lymphoma grade III patients, because usually these patients receive the same treatment regimens as patients with DLBCL, resulting in improved survival [20, 21]. One patient was assessed twice, at the first manifestation of DLBCL and at a relapse three-and-a-half years later. In the survival analysis only data on the first manifestation was used (n = 43). Ten patients were included in a previous analysis with several types of cancer combined [22].

Geriatric Assessment

Before participating in the study, informed consent was obtained. At baseline, the patients were prospectively assessed by trained nurses using the following tests: Mini Nutritional Assessment (MNA) [23], Groningen Frailty Indicator (GFI) [24], Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [25], and Mini Mental State Examination (MMSE) [26]. There were data missing for MNA (n = 2), but these could be reliable categorized based on the available data. The GFI, IQCODE, MMSE and MNA tests were pragmatically selected for performing a GA with a minimum of overlap between the domains and a maximum of 45 minutes to complete the interview. The MNA combines anthropometric measures with risk factors for malnutrition (disease, mental health and functional dependency, ingestive behaviour and subjective health) [27]. The MNA is a stepwise test and is comprised of two sections. First, there is the screening section (6 items). When the score is less than 12 points, indicating the possibility of malnutrition, the assessment section (12 items) is filled in. The GFI has been developed as a simple screening instrument for frailty and a case finder for elderly patients who would benefit from integrated (geriatric) care. The GFI consists of items on physical, cognitive, social and emotional functioning with a maximum score of 15 points. Patients scoring 4 or more points are considered to be frail (appendix). The IQCODE screens for cognitive decline over the last 10 years by interviewing family members or care givers, for which we used the short Dutch translation IQCODE-N [28]. The 16 items are rated on 5-point Likert scales, ranging from much improved to much worsened, and the average score is used in the analyses. In clinical settings, a cut-off score of 3.31 reasonably balances between sensitivity and specificity on the outcome of cognitive decline with higher scores indicating poorer cognition. The MMSE has been tested extensively and is considered to be a standard test for current cognitive function. Sensitivity of the MMSE for cognitive dysfunction is 88%, the specificity is 93% [29]. The cut-off point for poor cognition is 24 points or less. If indicated by the test results, a dietician or a geriatrician was consulted because of the importance of corrective action [30].

Laboratory values and other variables

Laboratory assessment before start of chemotherapy included serum albumin (cut-off < 35g/L); hemoglobin (cut-off < 6.8 mmol/L); creatinine (cut-off ≥ 100 µmol/L) and LDH (cut-off ≥ 250 U/L). These laboratory values were recorded retrospectively from the medical files by a trained registrar. Co-morbidity was registered by Charlson's comorbidity scoring system [31]. Another way of registration for comorbidity is possible with the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), but we did not choose for this system because it is more time consuming. Of course, we did not count NHL as comorbidity to calculate the Charlson comorbidity index, because NHL was the index disease. Performance status was registered by the scoring system ECOG/WHO or Karnofsky (KI) [32, 33]. Toxicity of chemotherapy in patients with early treatment withdrawal was retrospectively retrieved from the medical files and was scored according to the Common Terminology Criteria of Adverse Events (CTCAE) v. 4.03 [34].

Treatment and follow-up

According to current guidelines, patients with stage I (Ann Arbor stage [35]) were planned to be treated with at least three cycles of R-CHOP and patients with stages II-IV at least six cycles (according to scheme). When less than the number of cycles according to scheme were administered, this was considered as early treatment withdrawal.

The duration of follow-up was defined as the time between the date of the first GA until 1st January 2013 or the date of death. Vital status was checked with the nationwide population registries network at the end of the study period. These registries provide complete coverage of all deceased Dutch citizens. The cause of death was retrospectively retrieved from the medical files. Repeated assessment by GFI and MMSE was scheduled at the end of chemotherapy or at six months after start of chemotherapy.

Statistical analysis

Categorical variables are presented as numbers with percentages, chi-square tests were used to compare subgroups. We dichotomized stage in stage I and stage II-IV. Because of the small numbers of patients with an age-adjusted IPI of low risk and high risk we dichotomized the age-adjusted IPI in two categories: 0 and 1 risk factor (n = 24) versus 2 and 3 risk factors (n = 20). We also dichotomized MNA, GFI, IQ-code, MMSE, albumin, hemoglobin, creatinine and LDH according to the given cut-off scores.

To assess the association between GA scores and early treatment withdrawal, odds ratios (ORs) with 95% confidence intervals (CI) with p-values were estimated by univariate- and multivariate logistic regression analysis. Survival probabilities were estimated using Kaplan Meier curves and the log-rank test was used to test for differences in survival rates among subgroups of MNA, GFI, serum albumin, hemoglobin, serum creatinine, serum LDH and age-adjusted IPI. Association between baseline geriatric assessment scores and survival were estimated by hazard ratios (HRs) by univariate- and multivariate Cox proportional hazard analysis. Multivariate logistic regression models were adjusted for sex, age, comorbidity and univariate laboratory values with $p \leq 0.1$. The multivariate Cox regression models were adjusted for sex, age, comorbidity, age-adjusted IPI and univariate laboratory values with $p \leq 0.1$. Changes in GA-scores over time were analysed using the paired sample t-test. A p-value lower than 0.05 was considered significant. IBM-SPSS statistics 21 for Windows® (IBM-SPSS inc. Chicago, IL.) was used for statistical analyses.

Results

Characteristics and scores of the geriatric assessment are shown in table 1. The mean score (± SDs) of the MNA screening was 10.5 ± 2.6 and for the MNA assessment 13.6 ± 1.8. The mean scores of GFI, IQCODE and MMSE were 3.10 ± 0.14, 3.6 ± 2.7 and 27.7 ± 1.9 respectively.

Table 2 shows the baseline characteristics of the 44 patients treated with R-CHOP chemotherapy, of whom 43% were men. The mean age was 78 years (range 70–86), 46% were 80 years or older. The majority of patients either belonged to the low-intermediate risk category of the age-adjusted IPI (one risk factor) or to the high-intermediate risk category (two risk factors). No co-morbidities were documented in 11 (22%) patients. Most patients had diffuse large B-cell lymphoma (91%). The median follow-up was 46 months (range 0–101).

At baseline, 15 patients (34%) were at risk for malnutrition or were malnourished and 19 patients (43%) had a GFI score of four or more points. Albumin was low in 14 (32%) patients and low hemoglobin was seen in 11 (25%) patients. There were only a few patients with cognitive impairment by IQ-CODE and MMSE, 11% and 5% respectively. Creatinine and LDH were elevated in 13 (30%) and 38 (86%) patients respectively (Table 3).

Thirty-two (73%) patients received chemotherapy according to the protocol. Twelve (27%) patients failed to complete the intended number of chemotherapy cycles: 11 with stage II-IV and 1 with stage I. The most important reasons for early withdrawal were toxicity of chemotherapy (50% of cases), insufficient response, worsening of comorbidity and general condition.

Table 4 shows the association between geriatric assessment scores and laboratory variables for early treatment withdrawal. In the univariate analysis poor MNA and GFI scores, and a decreased value of hemoglobin were associated with early treatment withdrawal. In multivariate analysis, after adjustment for sex, age, comorbidity and univariate laboratory values with $p \leq 0.1$, poor MNA and GFI scores and low hemoglobin level maintained association with early treatment withdrawal: ORs 8.29 (95% CI: 1.24-55.6; p = 0.03), 9.17 (95% CI: 1.51-55.8; p = 0.02) and 5.41 (95% CI: 0.99-29.8; p = 0.05), respectively. According to the CTCAE, half of the patients with early treatment withdrawal (n = 12) had hematological toxicity grade 3 to 4. All 12 patients suffered from nonhematological toxicities such as mucositis, lung infection, depression, renal insufficiency, bad condition, atrial flutter, dysphagia, nausea, colonic- or gastric hemorrhage, and sepsis, see table 5. In a separate analysis, also adjusting for MNA and GFI, the MNA was no longer significantly associated with early treatment withdrawal, possibly reflecting that impaired nutritional status results in frailty (data not shown).

With respect to survival, 28 (65%) patients had died at the date of last follow-up. The Kaplan-Meier curves for survival, according to predefined cut-off scores, are shown in figure 2. Patients with abnormal MNA and GFI score, low

hemoglobin and elevated creatinine showed a significantly higher mortality risk. In univariate Cox regression analysis the age-adjusted IPI with 2-3 risk factors versus 0-1 risk factor showed a HR of 1.57 (95% CI: 0.74-3.31; p=0.24). In multivariate analysis (adjusted for sex, age, comorbidity, univariate laboratory values with $p \leq 0.1$ and age-adjusted IPI) abnormal GFI score and low hemoglobin predicted for mortality with HRs of 2.55 (95% CI: 1.07-6.10; p = 0.04) and 4.90 (95% CI: 1.76-13.7; p = 0.002), respectively, shown in table 6.

Most common cause of death was progression of NHL (50%). Four patients (15%) died because of toxicity of chemotherapy. Other causes were cardiovascular problems (12%), infectious problems (12%) or unknown (11%).

GFI and MMSE were repeated in only 13 patients at the end or 6 months after the start of chemotherapy; therefore meaningful analyses could not be performed.

Discussion

This prospective cohort study demonstrates that early treatment withdrawal after start of R-CHOP was associated with poor scores for MNA and GFI, and decreased levels of hemoglobin at the start of chemo-immunotherapy. An abnormal score for GFI and decreased level of hemoglobin were significantly associated with the risk of death, both in univariate and multivariate analyses. As the number of patients with cognitive impairment, measured by IQ-code and MMSE, was limited, no meaningful analyses could be performed in this regard.

It is important to realize that in this cohort of patients the hematologist decided to treat the patient with systemic therapy before GA was performed. The patients were considered fit enough for treatment with R-CHOP on clinical grounds. This probably explains the low number of patients with cognitive dysfunction as assessed by MMSE and IQ-CODE. The hematologist quite likely selected on the absence of obvious cognitive problems. Nevertheless, GA revealed considerable shortcomings in the test results of MNA and GFI, respectively in 34 and 43% of the patients. It is well accepted nowadays that a GA provides additional information to judgment by performance status and is predictive for the functional outcome in the elderly patient with cancer [12, 14].

Poor scores for MNA, GFI and anemia were associated with early withdrawal of systemic chemotherapy (inability to be treated according to scheme) and this pertains especially for the GFI and anemia. Most probably a poor score with MNA also reflects frailty. The GFI, a 15-items questionnaire (9 on physical functioning and 6 on psychosocial functioning), is an indicator for frailty, exemplified for example by a decline in self-management abilities [36]. Alternatively, the ADL and IADL questionnaires could be used. However, GFI also reflects nourishment, cognition, feelings of anxiety and depression. When frailty, defined by GFI or ADL/IADL, results in the inability to receive optimal chemo-immunotherapy, reduced survival can be expected as has been demonstrated in several studies [9, 15, 17, 37, 38). Shortcomings in IADL have been demonstrated to result in increased hematologic toxicity [39], overall grade 3-5 toxicity [40], early functional decline [41] and shorter survival [18]. The predictive model of Hurria et al on grade 3-5 toxicity also identified anemia as a risk factor [40] and moreover, anemia is part of the FLIPI risk score, albeit this score has been developed for follicular lymphomas [42, 43]. The present study showed that early treatment withdrawal was associated with toxicity of the R-CHOP regimen in 50% of the cases. Early withdrawal of systemic chemotherapy could be responsible for the reduced survival in this patients category, as also has been demonstrated in the analysis of a population-based cohort of patients aged 75 years or older with DLBCL [44]. Finally, shortcomings in MNA was found a risk factor for non-hematologic toxicity [39] as well as for early death [16].

To date, the most important prognostic value for survival is obtained by using the age-adjusted IPI [11], even in the present era in which a lot of immune-histochemical biomarkers have been investigated for additional prognostic significance [45]. Fine-tuning of the application of the IPI in the post rituximab era resulted in the so-called R-IPI [46] and for patients older than 70 years of age the E-IPI has been demonstrated to give more discriminative power in the low and low-intermediate risk groups [47]. Nevertheless, in other patient cohorts the standard IPI remained a valid predictor of outcome [48]. Others showed the absolute lymphocyte count to be an independent risk factor besides the R-IPI, ALC/R-IPI [49], or the comorbidity [50]. Especially in elderly patients, of whom the majority is not entered into clinical trials [51], population-based data [44] may provide additional insights for proper treatment decisions in this fast growing number of patients, as has been shown for comorbidity and IPI [50]. Therefore, the present study emphasizes the importance of a GA by showing that frailty by the GFI and low hemoglobin were predictive for the risk of early withdrawal of R-CHOP and mortality of patients over 70 years of age treated with R-CHOP. Notably, almost half of the patients (46%) in our study were 80 years or older and the median follow-up was 46 months, thereby augmenting the value of the data for elderly patients.

Some limitations have to be taken into account. Firstly, the cohort is small,

resulting in relatively wide confidence intervals. Secondly, a limited number of tests were selected to perform a GA, striving for a minimum need of time and a minimum of overlapping items between tests. We did not assess the response criteria standardized by Cheson [52], and therefore we could not analyze whether GA predicted for response. Thirdly, the selected patients underwent a GA after they were considered to be fit to undergo chemotherapy by their hematologist, thereby introducing selection bias. Despite these limitations the GA results revealed some interesting associations with early withdrawal of chemotherapy and mortality.

In conclusion, we found additional prognostic factors. MNA, GFI and hemoglobin were associated with early treatment withdrawal and GFI and hemoglobin were, independent of the age-adjusted IPI, predictive for an increased mortality risk. Further research in larger cohorts of elderly patients with non-Hodgkin lymphoma is needed for proper fine-tuning of prognostic factors besides the well known IPI. The value of GA to identify risk factors, suitable and elderly patients confined, is demonstrated with this study and practical judgment alone falls short in this regard. Whether appropriate interventions, based on identified risk factors by GA, can result in better outcome of treatment, should be investigated in future prospective studies. So far, the identification of GA-associated risk factors should be helpful for caution in the management strategy of the hematologist.

Table 1. Domains and measures of the Geriatric Assessment

Domain	Measure	No. of items	Description	Range of scores	Mean (SD)	Min-Max
Nutrition	MNA	6 (screening) 12 (assessment)	Identify patients at risk for malnutrition	0-14 (S) 0-16 (A) (higher score: better nutritional state)	10.5 (2.6) 13.6 (1.8)	4-14 9-16
Cognition	IQCODE	16	Screens for cognitive decline over the last 10 years by interviewing family members or care givers	1-5 (lower score: less cognitive decline)	3.10 (0.14)	3.00-3.63
	MMSE	20	Screens for cognitive dysfunction	0-30 (Higher score: better cognitive function)	27.7 (1.9)	23-30
Frailty	GFI	15	Screens for deterioration on physical, cognitive, and psycho-social items	0-15 (Higher score: more frailty)	3.6 (2.7)	0-11

Abbreviations: MNA, Mini Nutritional Assessment, a stepwise test: when the score in the screening section (S) is less than 12 points, indicating the possibility of malnutrition, the assessment section (A) is completed. With the assessment section, a total score of 24-30 points is indicative of being well-nourished, 17-23.5 points for being at risk of malnutrition, and a score of less than 17 points for being malnourished.; IQCODE, Informant Questionnaire on Cognitive Decline, ranging from much improved to much worsened, and the average score is used in the analyses; GFI, Groningen Frailty Indicator, with a maximum score of 15 points. Patients scoring 4 or more points are considered to be frail. MMSE, Mini Mental State Examination, where the cut-off point for poor cognition is 24 points or less. SD, standard deviation.

Table 2 Baseline characteristics of patients with NHL receiving R-CHOP regimen (n=44)*

	n (%)
Sex	
Male	19 (43)
Female	25 (57)
Age	
70-74 years	8 (18)
75-79 years	16 (36)
≥ 80 years	20 (46)
WHO-performance / Karnofski Index	
0 - (KI 90-100%)	31 (71)
1 - (KI 70-80%)	10 (23)
≥2 - (KI 30-60%)	3 (6)
Age-adjusted IPI	
0 - Low risk	3 (7)
1 - Low-intermediate risk	21 (47)
2 - High-intermediate risk	18 (41)
3 - High risk	2 (5)
Comorbidity (Charlson index)	
0	11 (25)
1	12 (27)
≥ 2	20 (46)
Unknown	1 (2)
Malignancy	
Diffuse large B-cell lymphoma (DLBCL)	40 (91)
Follicular lymphoma grade III	4 (9)
Stage	
Stage I	11 (25)
Stage II	11 (25)
Stage III	10 (23)
Stage IV	12 (27)

*One patient presented with stage I and three-and-a-half years later with stage II DLBCL and thus was registered twice.

Table 3. Abnormal baseline geriatric and laboratory assessment results (n=44)

Test	n (%)
MNA (Risk of) malnutrition*	15(34)
GFI (risk of) frailty (>4 points)	19 (43)
IQ-code Cognitive decline** (<3.31 points))	5 (11)
MMSE Cognitive dysfunction (<24 points)	2 (5)
Albumin Low (<35g/l)	14 (32)
Hemoglobin Low (<6.8mmol/L)	11 (25)
Creatinine Elevated (≥100 µmol/L)	13 (30)
LDH Elevated (≥250 U/L)	38 (86)

*:(Risk of) malnutrition defined as a score of ≤ 11 on the MNA screening section or less than 24 pts on the assessment section.
** (n=43).

Table 4. Geriatric and laboratory assessment scores according to failure to complete R-CHOP regimens (n=44)

	Chemotherapy					
	Completed n (%)	Not completed n (%)	**Univariate Analysis** odds ratio (95% CI)	**p-value**	**Multivariate Analysis*** odds ratio (95% CI)	**p-value**
MNA						
Well nourished	25 (78)	4 (33)				
(Risk of) malnutrition	7 (22)	8 (67)	7.14 (1.65-30.9)	0.008	8.29 (1.24-55.6)	0.03
GFI						
Not frail	22 (69)	3 (25)				
(Risk of) frailty	10 (31)	9 (75)	6.60 (1.47-29.7)	0.01	9.17 (1.51-55.8)	0.02
Albumin						
Normal	23 (72)	7 (58)				
Low (<35g/l)	9 (28)	5 (42)	1.83 (0.46-7.27)	0.39		
Hemoglobin						
Normal	27 (84)	6 (50)				
Low (<6.8 mmol/L)	5 (16)	6 (50)	5.40 (1.23-23.7)	0.03	5.41 (0.99-29.8)	0.05
Creatinine						
Normal	23 (72)	8 (67)				
Elevated (≥100 µmol/L)	9 (28)	4 (33)	1.28 (0.31-5.32)	0.74		
LDH						
Normal	3 (9)	3 (25)				
Elevated (≥250 U/L)	29 (91)	9 (75)	0.31 (0.05-1.82)	0.19		

Odds ratios were calculated using logistic regression.
Completed: **s**tage I number of cycles ≥ 3; stage II, III and IV number of cycles ≥ 6.
*Adjusted for sex, age, comorbidity and univariate laboratory values with p ≤ 0.1.
The MMSE and IQ-CODE were not taken into account due to the low variability in scores.

Table 5. Treatment related adverse events of 12 patients with early treatment withdrawal.

Toxicity type*	Grade 3-5	Grade 3	Grade 4	Grade 5
	no (%)	no (%)	no (%)	no (%)
Hematologic				
Leukocytopenia	5 (42)	4 (25)	1 (8)	
Anemia	2 (17)	2 (17)		
Trombocytopenia	2 (17)	1 (8)	1 (8)	
Nonhematologic				
Mucositis	2 (17)	2 (17)		
Lung infection	3 (25)			3 (25)
Renal insufficiency	1 (8)	1 (8)		
General condition (fragility)	1 (8)			1 (8)
Atrial flutter	1 (8)	1 (8)		
Dysphagia	1 (8)	1 (8)		
Nausea	2 (17)	2 (17)		
Colonic hemorrhage	1 (8)		1 (8)	
Gastric hemorrhage	1 (8)			1 (8)
Sepsis	3 (25)	1 (8)		2 (17)
Ileus	1 (8)	1 (8)		

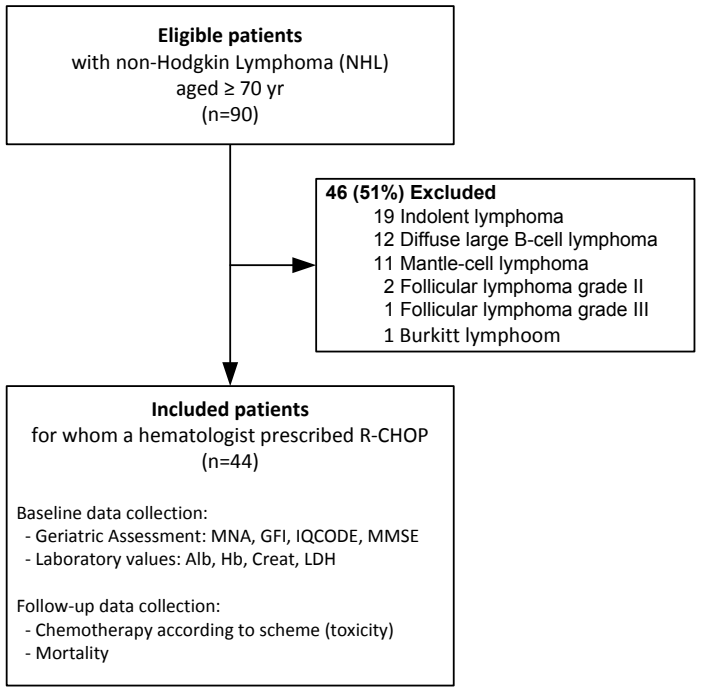
* According to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (34)

Table 6. Geriatric and laboratory assessments in relation to all cause mortality in patients with NHL treated with R-CHOP chemotherapy (n=43*)

	Alive n (%)	**Deceased** n (%)	**Univariate Analysis** hazard ratio (95%CI)	**p-value**	**Multivariate Analysis**** hazard ratio (95%CI)	**p-value**
MNA						
Well nourished	12 (80)	16 (57)				
(Risk of) malnutrition	3 (20)	12 (43)	2.11 (0.98-4.54)	0.056	1.46 (0.56-3.78)	0.44
GFI						
Not frail	11 (73)	13 (46)				
(risk of) frailty	4 (27)	15(54)	2.39 (1.11-5.14)	0.03	2.55 (1.07-6.10)	0.04
Albumin						
Normal	11 (73)	19 (68)				
Low (<35g/l)	4 (27)	9 (32)	1.83 (0.81-4.16)	0.15		
Hemoglobin						
Normal	14 (93)	18 (64)				
Low (<6.8 mmol/L)	1 (7)	10 (36)	2.45 (1.12-5.37)	0.03	4.90 (1.76-13.7)	0.002
Creatinine						
Normal	12 (80)	19 (68)				
Elevated (≥100 µmol/L)	3 (20	9 (32)	2.23 (0.98-5.12)	0.057	1.84 (0.70-4.86)	0.22
LDH						
Normal	3 (20)	3 (11)				
Elevated (≥250 U/L)	12 (80)	25(89)	0.92 (0.27-3.11)	0.90		
IPI						
Low risk + Low-intermediate risk	9 (60) 6 (40)	14 (50) 14 (50)	1.57 (0.74-3.31)	0.24		
High-intermediate risk + High risk						

HRs were calculated using Cox regression analysis.
* One patient was registered twice because of a relapse after three-and-a-half years, only the first assessment was used in the survival analysis.
** Adjusted for sex, age, comorbidity, age-adjusted IPI and univariate laboratory values with p ≤ 0.1.

Figure 1. Flow-diagram of the study



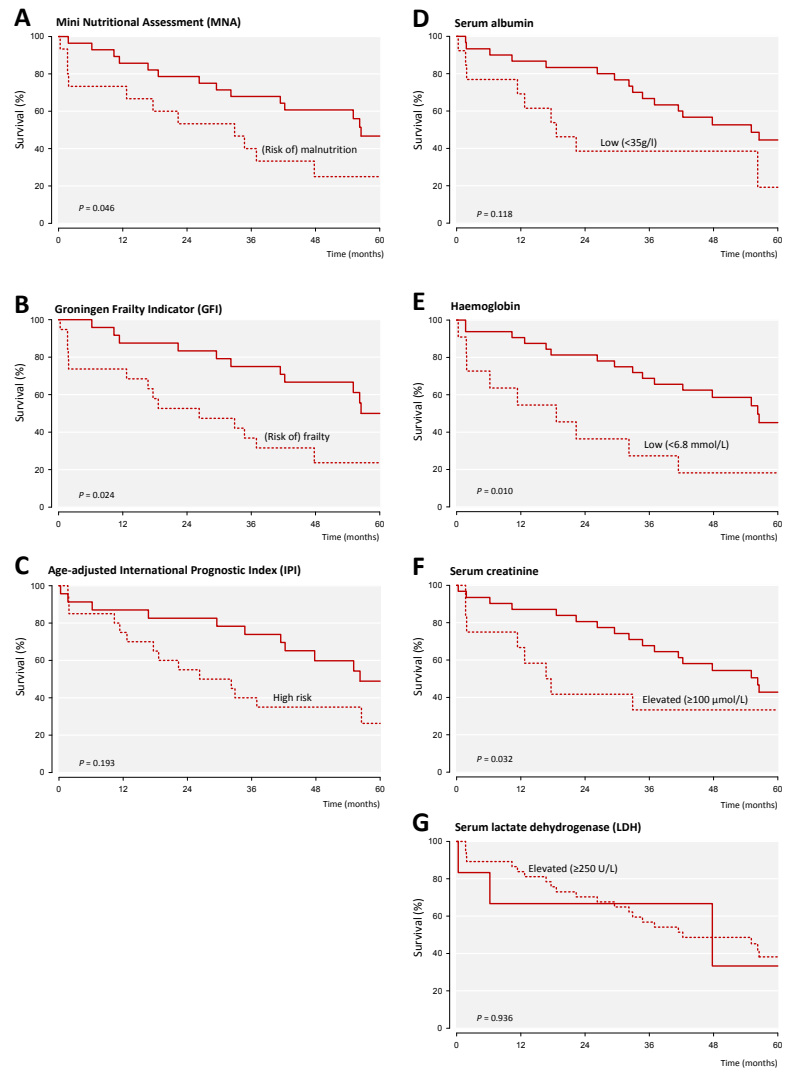


Figure 2.
Kaplan–Meier curves of overall survival during up to 60 months (i.e. 4 yr, until 31 December 2012) follow-up in patients with NHL according to categories of: [A] MNA, [B] GFI, [C] age-adjusted IPI, [D] albumin, [E] hemoglobin, [F] creatinine, and [G] LDH.
P-values by log-rank tests.

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