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Independent prognostic effect of co-morbidity in lymphoma patients: Results of the population-based Eindhoven Cancer Registry

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Abstract

The prevalence of co-morbidity among elderly lymphoma patients is associated with a decrease in the use of chemotherapy. This study assessed the independent prognostic effect of co-morbidity in 1551 unselected lymphoma patients, diagnosed between 1995 and 2001 in the area of the population-based Eindhoven Cancer Registry. The prevalence of serious co-morbidity was 58% for patients with Hodgkin's disease (HD) who were over 60 years of age and 66% for patients with non-Hodgkin's lymphoma (NHL) who were over 60 years of age. The administration of chemotherapy declined in the presence of co-morbidity for elderly patients with early-stage HD and elderly patients with aggressive NHL. Co-morbidity was associated with a 10–20% decline in 5-year survival. Whether less frequent application of chemotherapy in the presence of co-morbidity is justified as far as complications, prognosis and quality of life are concerned requires further investigation.

Keywords: Co-morbidity; Lymphoma; Elderly; Treatment; Survival

1. Introduction

Since age and co-morbidity are frequently used as selection criteria for clinical trials, the results may not be valid for all lymphoma patients [1]. Population-based survival rates are generally lower for both Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) compared with those reported by referral centres or clinical trials, since population-based series probably include more elderly patients and patients with serious co-morbidity [2–5].

For patients with NHL in particular, which is characterised by a steeply increasing incidence with age, co-morbidity is of major importance since more than 50% of all elderly patients suffer from one or more other serious diseases at the time of diagnosis of NHL [6]. For elderly NHL patients in the Netherlands, staging is frequently incomplete and treatment is not adequate [7,8], tolerance of chemotherapy is decreased [9] and the possibility of complete remission and long-term survival is generally low [10–12].

Presumably this is all due to co-morbidity and diminished organ reserves with subsequent impaired tolerance of chemotherapeutic agents. Co-morbidity can influence therapeutic decision-making; it may necessitate the modification of a chosen therapy and, if serious enough, it might be an independent prognostic factor [6,8,13]. In this population-based study the prevalence of co-morbidity in lymphoma patients was determined and the

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influence of age and co-morbidity on choice of treatment and long-term survival was assessed.

2. Patients and methods

The Eindhoven Cancer Registry (ECR) collects data on all patients with newly diagnosed cancer in the Dutch province of North Brabant and the northern part of the adjacent province of Limburg, which have a total of more than 2 million inhabitants.

The trained registry officers actively collect data about diagnosis and treatment from clinical records upon notification of pathological laboratories and medical registration offices. The completeness of the Dutch cancer registries is more than 95% [14]. Since 1993 data about co-morbidity has been obtained from the medical records, according to an adapted version of the list drawn up by Charlson and colleagues [13]. Only co-morbid conditions with potentially negative prognostic effects were included in this study (Table 1). Cardiovascular, cerebrovascular and other vascular diseases were also included after a vascular event or vascular surgery. The medical record is generally regarded as the most complete source of information on the patient's past and current health status [15,16]. In the period 1995–2001, 295 patients with HD and 1249 patients with NHL older than 15 years were diagnosed. Patients with uncommon lymphomas (mainly Waldenstrom's disease, Sezary's syndrome and mycosis fungoides) ($n = 64$, 4%) and 238 (15%) with lymphomas not otherwise specified were excluded from this study.

Patients with HD were subdivided into early-stage (IA–IIA) and advanced-stage (IIB–IVB) disease, according to the Ann Arbor classification [17]. Patients with NHL were subdivided into indolent *versus* aggressive lymphoma according to the REAL classification by translation of the registry data, which were originally recorded according to the Working Formulation [18].

Table 1
Classification of co-morbidity, according to an adapted version of Charlson and colleagues [13]

Chronic obstructive pulmonary disease (COPD)
Cardiovascular diseases:
Myocardial infarction, cardiac decompensation, angina pectoris, intermittent claudication, abdominal aneurysm, peripheral arterial disease
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Hypertension
Diabetes mellitus
Previous malignancies (except basal cell skin carcinoma and carcinoma *in situ* of the cervix)
Other:
Connective tissue diseases, Besnier–Boeck disease, Wegener's disease, systemic lupus erythematosus (SLE)
Rheumatoid arthritis (only severe)
Kidney diseases (chronic glomerulonephritis and pyelonephritis)
Bowel diseases (Crohn's disease, ulcerative colitis)
Liver diseases (cirrhosis, hepatitis)
Dementia
Tuberculosis
Chronic infections

Treatment guidelines were established at regular multidisciplinary meetings within the framework of the regional comprehensive cancer centre and were often derived from trials of the European Organisation for Research and Treatment of Cancer (EORTC) or the Dutch Haemato-Oncology for Adults Association (HOVON). In general, patients with early-stage HD received 4–6 cycles of chemotherapy (usually doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine (ABVD) or epirubicin, bleomycin, vinblastine, prednisolone (EBVP)) followed by involved field irradiation (either within or according to the ongoing EORTC trials for early-stage HD). Patients with advanced HD generally received chemotherapy (usually 6–8 cycles of mustine, vincristine (Oncovin), procarbazine, prednisolone/ABVD (MOPP/ABVD)) followed by involved field irradiation. Patients with early-stage indolent NHL usually received involved field irradiation, while patients with advanced stages generally followed a wait-and-see policy or chemotherapy (usually oral chlorambucil or 4–8 cycles of cyclophosphamide, vincristine (Oncovin), prednisolone (COP)) with or without involved field irradiation. Patients with stage I aggressive NHL generally received 3 cycles of cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy followed by involved field irradiation, whereas patients with stages II–IV generally received 6–8 cycles of CHOP, with or without involved field irradiation. Patients with lymphoblastic NHL received the same systemic treatment as those with acute lymphoblastic leukaemia. For the analyses, treatment was classified as 'chemotherapy (with or without radiotherapy)', 'radiotherapy alone' or 'other (which includes surgery) or no treatment'.

This study analysed the age-specific ($\leqslant$60 years *versus* >60 years) prevalence of co-morbidity among patients with HD, indolent NHL and aggressive NHL and the association between co-morbidity and systemic chemotherapy.

Vital status was assessed up to 1st January 2004. In addition to passive follow-up in the hospitals, this information was also obtained from the municipal registries in the registration area and the Central Bureau for Genealogy. The latter registers all deceased Dutch citizens via the civil municipal registries. In this way, information on patients who had moved outside the registry area was also obtained. Patients who died outside the Netherlands were wrongly considered as 'being alive'. However, the proportion of these patients was estimated to be only 0.5%. Crude survival was analysed, according to age, sex, stage, the presence of co-morbidity and the

use of systemic chemotherapy. Multivariable analyses were performed using a Cox regression model. The independent prognostic effect was first estimated in a model including age, sex, stage and co-morbidity. Then treatment with systemic chemotherapy was included in the model to determine whether the prognostic effect of co-morbidity could be explained by withholding chemotherapy.

Since death rates from causes other than cancer increase with age, relative survival rates for each age group were calculated as an estimate of disease-specific survival. Survival of cancer patients was adjusted for mortality from all causes of death in the background population with the same age structure. Mortality in the background population was estimated from life tables for regional male and female populations [19].

3. Results

3.1. Prevalence of co-morbidity

The general characteristics of the patients are listed in Table 2. Co-morbidity was prevalent in 58% of patients over 60 years of age with HD and 66% of patients over 60 years of age with NHL. Cardiovascular disease and hypertension were the most common co-morbid conditions. The prevalence of co-morbidity correlated markedly with increasing age ($P < 0.0001$). The prevalence of co-morbidity did not correlate with histology or stage (data not shown).

3.2. Co-morbidity and application of chemotherapy

For elderly patients with early-stage HD, chemotherapy was given less frequently and radiotherapy alone was applied more frequently than among younger patients ($P = 0.05$). For elderly patients, the administration of chemotherapy declined further in the presence of co-morbidity ($P = 0.07$). No difference in chemotherapy between patients with or without co-morbidity was observed for patients with advanced-stage HD (Fig. 1(a)).

For elderly patients with aggressive NHL, chemotherapy was given less frequently and radiotherapy alone was applied more frequently than among younger patients ($P < 0.0001$). A decline in the administration of chemotherapy with co-morbidity was also observed for patients with aggressive NHL (age $\leqslant$ 60 years: $P = 0.002$; age > 60 years: $P = 0.04$) (Fig. 1(b)).

3.3. Co-morbidity as prognostic factor

For HD patients the 5-year crude survival rate declined significantly with age (from 88% for patients aged 60 years or less to 46% for those over 60 years of age) (Table 3). The 5-year relative survival rate also decreased with age (from 87% for patients aged 60 years or less to

Table 2
General characteristics of 294 Hodgkin's disease (HD) and 1249 non-Hodgkin's lymphoma (NHL) patients diagnosed in 1995–2001

	Number (%) of patients			
	HD		NHL	
	⩽60 years ($n = 238$)	>60 years ($n = 57$)	⩽60 years ($n = 559$)	>60 years ($n = 690$)
Gender				
Male	140 (59)	28 (49)	326 (58)	376 (54)
Female	98 (41)	29 (51)	233 (42)	314 (46)
Stage				
I/II	180 (76)	33 (58)	255 (46)	303 (44)
III/IV	53 (22)	21 (37)	282 (50)	322 (47)
Unknown	5 (2)	3 (5)	22 (4)	65 (9)
REAL classification				
Indolent			206 (48)	219 (52)
Aggressive			353 (42)	471 (58)
Co-morbidity[a]				
No co-morbidity	187 (79)	24 (42)	376 (67)	227 (34)
COPD	12 (5)	8 (14)	21 (4)	61 (9)
Cardiovascular	4 (2)	14 (25)	19 (3)	149 (22)
Hypertension	7 (3)	12 (21)	38 (7)	140 (20)
Diabetes mellitus	5 (2)	8 (14)	17 (3)	73 (11)
Other malignancy	3 (1)	3 (5)	17 (3)	88 (13)
Other	8 (3)	7 (12)	34 (6)	67 (10)
Unknown	13 (5)	1 (2)	47 (8)	45 (7)

COPD, chronic obstructive pulmonary disease.
[a] Total > 100%, because some patients suffered from 2 or more co-morbid conditions.

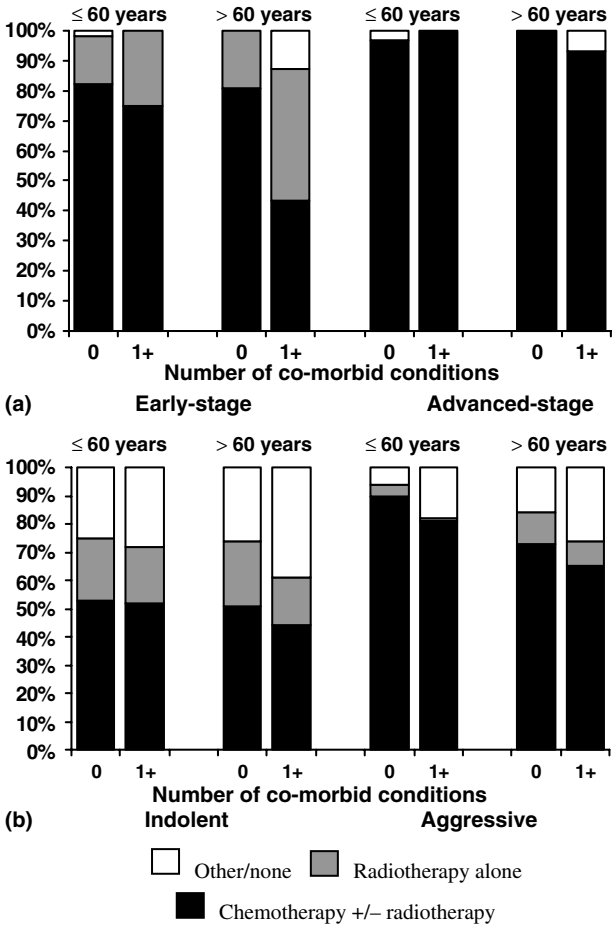

Fig. 1. Treatment of lymphoma patients, according to tumour type, stage, age and presence of co-morbidity (none *versus* one or more concomitant diseases). (a) Hodgkin's disease. (b) Non-Hodgkin's lymphoma.

54% for those older than 60 years). In multivariable analysis, age (hazard ratio 6.5) was an independent prognostic factor. The number of patients was too small to analyse the prognostic influence of the specific co-morbid conditions.

For patients with indolent NHL 5-year crude survival declined from 79% for patients aged 60 years or less to 48% for those older than 60 years (Table 4). Relative survival rates declined from 75% to 45%. Presence of co-morbidity also clearly decreased survival rates in both age groups. For younger patients the need for chemotherapy was associated with decreased survival. In multivariable analysis, age (hazard ratio 2.4), co-morbidity (hazard ratio 1.7) and chemotherapy (hazard ratio 1.5) were independent adverse prognostic factors. The presence of chronic obstructive pulmonary disease (COPD), in particular, appeared to have a strong prognostic relevance (hazard ratio 3.6).

For patients with aggressive NHL 5-year crude survival declined from 62% for patients aged 60 years or less to 31% for those older than 60 years (Table 5). The 5-year relative survival rate was 58% for patients aged 60 years or less and 30% for patients older than 60 years. For those aged 60 years or more survival also declined with co-morbidity from 43% for patients without co-morbidity to 18% for patients with two or more co-morbid conditions. The use of chemotherapy improved survival from 53% to 63% for patients aged 60 years or less and from 18% to 38% for those older than 60 years. In multivariable analysis, age (hazard ratio 2.0), stage (hazard ratio 2.1), presence of two or more co-morbid conditions (hazard ratio 1.4) and administration of chemotherapy (hazard ratio 0.5) were independent prognostic factors.

Table 3
Uni- and multivariable[a] analysis of crude survival for patients with Hodgkin's disease

	Univariable[c]				Multivariable	
	⩽60 years		>60 years		All ages	
	5 years % (95% CI)	*P*	5 years % (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age (years)	88 (84–93)		46 (33–59)	<0.0001	6.5 (3.8–11.2)	<0.0001
Gender						
Male[b]	85 (79–92)		42 (23–60)		1.0	
Female	92 (87–98)	0.13	50 (32–69)	0.7	0.8 (0.5–1.4)	0.4
Stage						
I/II[b]	91 (86–95)		47 (30–65)		1.0	
III/IV	78 (66–90)	0.009	52 (31–74)	0.8	1.5 (0.9–2.8)	0.2
Co-morbidity						
No[b]	90 (86–95)		57 (37–78)		1.0	
Yes	80 (66–93)	0.10	40 (22–57)	0.9	1.1 (0.9–1.3)	0.11
Chemotherapy						
No[b]	92 (83–99)		31 (09–54)		1.0	
Yes	87 (83–92)	0.6	52 (37–68)	0.10	0.8 (0.4–1.5)	0.5

CI, confidence interval.
[a] Adjusted for all listed variables.
[b] Reference category.
[c] Crude actuarial 5-year survival.

Table 4
Uni- and multivariable[a] analysis of crude survival for patients with indolent non-Hodgkin's lymphoma

	Univariable[c]				Multivariable	
	⩽60 years		>60 years		All ages	
	5 years % (95% CI)	*P*	5 years % (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age (years)	79 (72–85)		48 (40–56)	<0.0001	2.4 (1.6–3.5)	<0.0001
Gender						
Male[b]	75 (65–85)		48 (36–60)		1.0	
Female	82 (74–90)	0.5	47 (37–58)	0.3	1.1 (0.8–1.6)	0.5
Stage						
I[b]	86 (74–98)		73 (59–86)		1.0	
II/IV	76 (68–84)	0.3	41 (31–51)	0.005	1.6 (1.0–2.6)	0.05
Co-morbidity						
No[b]	83 (76–90)		58 (46–70)		1.0	
Yes	65 (50–80)	0.07	41 (30–51)	0.02	1.7 (1.2–2.5)	0.003
Chemotherapy						
No[b]	89 (81–96)		53 (42–63)		1.0	
Yes	70 (60–79)	0.003	42 (30–54)	0.4	1.5 (1.0–2.1)	0.04

CI, confidence interval.
[a] Adjusted for all listed variables.
[b] Reference category.
[c] Crude actuarial 5-year survival.

Table 5
Uni- and multivariable[a] analysis of crude survival for patients with aggressive non-Hodgkin's lymphoma

	Univariable[c]				Multivariable	
	⩽60 years		>60 years		All ages	
	5 years % (95% CI)	*P*	5 years % (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age (years)	62 (56–67)		31 (27–36)	<0.0001	2.0	<0.0001
Gender						
Male[b]	63 (57–70)		28 (22–34)		1.0	
Female	59 (50–68)	0.9	37 (30–44)	0.5	0.9	0.3
Stage						
I[b]	83 (74–92)		50 (41–59)		1.0	
II/IV	57 (50–63)	0.0006	24 (18–30)	<0.0001	2.1	<0.0001
Number of co-morbid conditions						
No[b]	64 (57–70)		43 (35–52)		1.0	
1	59 (46–72)		32 (24–39)		1.1	0.5
2+	50 (29–71)	0.4	18 (10–25)	<0.0001	1.4	0.006
Chemotherapy						
No[b]	53 (38–69)		18 (11–24)		1.0	
Yes	63 (57–69)	0.1	38 (33–44)	<0.0001	0.5	<0.0001

CI, confidence interval.
[a] Adjusted for all listed variables.
[b] Reference category.
[c] Crude actuarial 5-year survival.

The presence of cardiovascular disease had the strongest prognostic effect (hazard ratio 1.9).

4. Discussion

In this population-based study a high prevalence of co-morbidity (>60%) was observed among elderly lymphoma patients, as has been reported previously [6]. The most common co-morbid conditions were cardiovascular diseases and hypertension. This study used a slightly modified version of the classification of Charlson. Within the framework of the Eindhoven Cancer Registry it was not feasible to register severity of co-morbidity, but only to record serious co-morbid conditions with possible prognostic impact. Hypertension,

which has been shown to be a prognostic factor in some previous studies [20–22] was also included. Because of the small numbers of patients in each subgroup co-morbidity was classified as absent/present, except for aggressive NHL. In this subgroup, the number of patients was large enough to classify co-morbidity as 'no co-morbidity', 'one co-morbid condition' and 'at least two co-morbid conditions'. The completeness and accuracy of the data on co-morbidity were validated using a series of 400 consecutive NHL patients. Co-morbidity scored by the registry team was compared with that scored by a surgeon together with an epidemiologist. There was some under-registration of co-morbidity in the cancer registry, especially for cardiovascular diseases. This means that the group of patients classified as having 'no co-morbidity' in this study probably contains some patients who have co-morbid conditions, though of a less severe nature. Therefore, it is likely that the effects of co-morbidity are somewhat stronger than those presented in this study.

Older patients with HD or aggressive NHL received chemotherapy less often than did younger patients. In the presence of co-morbidity, the percentage of patients receiving chemotherapy declined among older patients with early-stage HD or aggressive NHL. This effect may be underestimated, because there was no information collected on dose reduction or delay of chemotherapy. The decrease in chemotherapy among older patients with NHL has also been reported for another area of the Netherlands [8]. The sharp decline in chemotherapy in the presence of co-morbidity in elderly patients with early-stage Hodgkin's disease is very likely due to the fact that radiotherapy offers a good alternative treatment for these patients. Our findings are in line with previous studies, which also demonstrated that cancer patients with extensive co-morbidity are often treated less aggressively, independent of the effects of age and stage [23–28]. Interestingly, irrespective of the presence of co-morbidity, advanced age itself caused physicians to refrain from systemic chemotherapy. Apparently co-morbidity is not the only reason why elderly patients undergo systemic chemotherapy less frequently. Application of a comprehensive geriatric assessment (CGA) might determine which treatment is most appropriate for the individual patient, beyond age and co-morbidity. Systemic chemotherapy, however, offers the best chance of cure for most patients with both HD and aggressive NHL. Therefore, the reduced use of chemotherapy obviously has an adverse prognostic impact [3,29], especially since aggressive NHL in elderly patients is reported to have a aggressive behaviour [30].

For patients with indolent NHL, the administration of chemotherapy was associated with decreased survival. This can probably be explained by the fact that those patients who have a disease with a more indolent clinical course and a subsequently favourable prognosis are candidates for 'watchful-waiting'. This 'watchful-waiting' strategy has been described recently as appropriate initial policy for patients with asymptomatic indolent lymphoma [31]. Thus, the use of chemotherapy is frequently associated with a more aggressive biological behaviour and the resulting survival curves predominantly reflect the natural behaviour of this disease. The fact that the adverse prognostic effect of administration of chemotherapy in this study was independent of age, stage and co-morbidity is in line with this reasoning.

For all subgroups of lymphoma, age and co-morbidity were both independent prognostic factors. It is known that increasing age is associated with decreased organ reserves and decreased tolerance to treatment with increased risk of side-effects, even in the absence of co-morbidity. Since age was an independent prognostic factor, variables other than co-morbidity may play a role, such as performance status, lactate dehydrogenase level, number or extranodal sites, presence of B symptoms, decreased organ reserves, or psychological and social factors. Unfortunately, these factors were not routinely available for analysis in the Eindhoven Cancer Registry. In the United States, performance status was found to be a prognostic factor independent of co-morbidity [32,33].

Since we adjusted for 'administration of chemotherapy', the dismal prognosis for elderly patients and those with co-morbidity cannot be explained fully by the withholding of systemic chemotherapy. The negative influence of co-morbidity on survival of cancer patients might be due to several mechanisms: the increased risk of death due to the co-morbid condition itself, more contra-indications for other (anti-cancer) treatments, more indications for dose reduction and a higher rate of treatment-related complications, such as infections and cardiovascular events. Data on dose-reduction, number of cycles given and treatment complications were not available in this study based on data from the Eindhoven Cancer Registry, but presumably these phenomena play a major role in the decreased survival rate of patients with co-morbidity.

Whether the shift towards less frequent administration of chemotherapy for elderly lymphoma patients with co-morbidity is justified as far as complications, prognosis and quality-of-life are concerned requires further investigation. The major limitation of this retrospective study is the fact that the quality of data depends on the data that are available in the medical records. Therefore, future prospective studies should also evaluate co-morbidity as a prognostic factor, independent of the International Prognostic Index (IPI).

Conflict of interest statement

None declared.

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