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ORIGINAL ARTICLE

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Prevalence of co-morbidity and its relationship to treatment among unselected patients with Hodgkin's disease and non-Hodgkin's lymphoma, 1993–1996

Abstract A population-based series of patients with cancer is likely to comprise more patients with serious co-morbidity than clinical trials because of restrictive eligibility criteria for the latter. Since co-morbidity may influence decision-making, we studied the age-specific prevalence of co-morbidity and its relationship to applied treatment. Data on all 194 patients with Hodgkin's disease (HD) and on 904 patients with non-Hodgkin's lymphoma (NHL) diagnosed between 1993 and 1996 were derived from the Eindhoven Cancer Registry. In the age-group below 60 years, 87% of patients with HD and 80% with NHL did not have a co-morbid condition. The prevalence of serious co-morbidity was 56% for patients with Hodgkin's disease who were 60 years and over and 43% and 61% for non Hodgkin patients who were 60–69 years and 70 years and over, respectively. The most common co-morbid conditions were cardiovascular disease (18%), hypertension (13%), chronic obstructive pulmonary disease (COPD; 13%), and diabetes mellitus (10%) for elderly Hodgkin's patients. For non-Hodgkin's patients of 60–69 years and 70 years and over, cardiovascular disease (15 and 22%, respectively), hypertension (14 and 14%, respectively), COPD (6 and 10% respectively), and diabetes mellitus (8 and 10%, respectively) were the most prevalent co-morbid conditions. The presence of co-morbidity was not related to stage or grade of disease at diagnosis. In the presence of co-morbidity, 50% less chemotherapy was administered to elderly patients with Hodgkin's disease and 10–15% less to elderly patients with non-Hodgkin's lymphoma. The presence of co-morbidity was associated with a decreased overall survival within the first 4 months after diagnosis in both Hodgkin's disease and non-Hodgkin's lymphoma for all age-groups. In conclusion, serious co-morbidity was found for more than half of all lymphoma patients who were 60 years and older. Elderly patients with serious co-morbidity received chemotherapy less often, which is likely to affect survival adversely, as was indicated by a decreased survival within the first 4 months after diagnosis.

Key words Co-morbidity · Elderly · Hodgkin · Lymphoma · Registry

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Introduction

Although numerous studies report successful treatment for the great majority of patients with Hodgkin's disease (HD), population-based survival rates are generally lower, in part because they probably include more older patients with serious co-morbidity [21, 24]. For patients with non-Hodgkin's lymphoma (NHL), characterized by a steeply increasing incidence with age, co-morbidity will be of even greater importance because 50% of all patients are >60 years. For elderly NHL patients staging is frequently incomplete and treatment is not adequate [6, 12], tolerance for combination chemo-

therapy is decreased [23], and chances for complete remission and long-term disease-free survival are generally lower [7, 20, 22] – all presumably due to the presence of co-morbidity.

Co-morbidity may have several clinical implications. It can influence therapeutic decision-making, it may necessitate modifications of and/or interact negatively with a chosen therapy, and it might also be an independent prognostic factor in itself, regardless of the therapy chosen [5, 6]. Co-morbidity may be a selection criterion for experimental studies with restrictive eligibility criteria, thus biasing the results with respect to the general health-care environment. Furthermore, certain co-morbid conditions may be associated with an increased risk for the development of NHL, suggesting an etiological relationship [4, 11].

At the request of clinicians, the Eindhoven Cancer Registry has been collecting data on relevant co-morbid diseases for all cancer patients since 1993. The validated index of co-morbidity developed by Charlson and colleagues was used, which implies that only conditions that are likely to have an independent, negative prognostic value were included [5]. In this study the age-specific prevalence of co-morbidity for patients with both HD and NHL and its relationship to applied treatment were analyzed.

Patients and methods

The Comprehensive Cancer Centre South (I.K.Z.), covering an area with more than two million inhabitants since 1988, collects data on patients with newly diagnosed cancer in the Dutch province of North Brabant and the northern part of the adjacent province of Limburg. Between 1993 and 1996, 194 patients with HD and 904 patients with NHL were diagnosed and treated in 16 general hospitals and two large radiotherapy institutes that collaborate within the I.K.Z.

The registry officers actively collect data on diagnosis and treatment from clinical records in the various hospitals within 6 months of diagnosis. Since 1993 co-morbidity has also been recorded, according to an adapted version of the list presented by Charlson and colleagues [5]. Only prognostically relevant co-morbid diseases were included (Table 1). The following sources were used: medical history, correspondence, current medication, and preoperative assessments. With respect to the assessment of co-morbidity, the following rules were applied: chronic obstructive pulmonary disease (COPD), hypertension, and diabetes mellitus were included only if the patient was receiving current medical treatment. Cardiovascular, cerebrovascular, and other vascular diseases were also included after a vascular event or vascular surgery. Another cancer (excluding basal cell carcinoma of the skin and carcinoma in situ) had to have been diagnosed within the previous 10 years. During 1996 and 1997, the completeness and accuracy of the data on co-morbidity were checked in a series of consecutive patients with lung ($n=125$), endometrial ($n=200$), and prostate cancer ($n=150$) [13, 14, 18]. The attending specialist was asked to score co-morbidity according to the same list. Recording of co-morbidity was correct for about 80% of patients with lung or prostate cancer and for 90% of those with endometrial cancer. Under-registration by registry personnel was found mainly for cardiac and other vascular diseases, because terms such as CABG (coronary artery bypass grafting) had sometimes been disregarded, mainly in the beginning period.

Table 1 Classification of co-morbidity, according to an adapted version of Charlson et al. [5]

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

Patients with HD were subdivided into early-stage (IA-IIA) and advanced-stage disease (IIB-IVB), according to the Ann Arbor classification [3]. Patients with NHL were subdivided into low-grade versus intermediate/high-grade histology, according to the Working Formulation [16].

The registry officers did not record data regarding which type of schemes of chemotherapy were given; however, treatment guidelines were advocated by regular multidisciplinary meetings within the framework of the regional comprehensive cancer centre. In general, patients with early-stage HD without symptoms received mantle-field or inverted Y-field irradiation, while more extensive irradiation with or without chemotherapy was given in the presence of symptoms. Patients with advanced HD generally received chemotherapy, usually MOPP/ABVD, frequently followed by iceberg irradiation. Patients with early-stage low-grade NHL usually received involved-field irradiation, while for patients with advanced stages generally a wait-and-see policy was followed or chemotherapy (usually COP) was given, with or without involved-field irradiation. Patients with intermediate and high grade NHL generally received CHOP or CNOP chemotherapy, with or without involved field irradiation. Patients with lymphoblastic NHL received the same chemotherapeutic treatment as in acute lymphoblastic leukemia.

We analyzed the age-specific prevalence of co-morbidity for both HD and NHL patients. For HD we analyzed the association between co-morbidity and choice of treatment according to stage of the disease, for NHL according to grade. Grade remained unclassified for 254 NHL patients who had extranodal and skin lymphomas. Differences between groups were determined using the chi-square test. Since follow-up results were available for only the first 4 months, survival within 4 months was calculated according to age-group.

Results

NHL was diagnosed five times more often than HD. The mean age of HD patients was 40 years (range 5–81), NHL patients 61 years (range 16–93). NHL and HD were more frequently diagnosed among males, at 57% and 62%, respectively. Co-morbidity was more prevalent among male ≥60 years (63% and 55%) than

Table 2 Age-specific prevalence of co-morbidity[a] among 194 HD patients and 904 NHL patients diagnosed in 1993–1996 in the south-eastern Netherlands

	Hodgkin's disease		Non-Hodgkin's lymphoma		
	< 60 years (%)	≥ 60 years (%)	< 60 years (%)	60–69 years (%)	≥ 70 years (%)
No co-morbidity	87	44	80	57	39
COPD	6	13	2	6	10
Cardiovascular	1	18	3	15	22
Cerebrovascular	1	–	1	3	6
Hypertension	3	13	6	14	14
Diabetes mellitus	2	10	1	8	10
Other malignancy	1	3	4	9	14
Other	3	15	5	9	12
(n =)	(155)	(39)	(372)	(222)	(310)

[a] Total is >100% because some patients suffered from two or more co-morbid conditions.

female (47% and 52%) patients with HD and NHL, respectively. Subdivision of NHL according to grade was as follows: low-grade 22%, intermediate-grade 43%, high-grade 7%, and unknown 28%. Subdivision of HD according to stage was as follows: early-stage 56%, advanced-stage 37%, and unknown 7%. Cardiovascular disease was the most common co-morbid condition in both HD and NHL, with a prevalence of almost 20% in patients aged 60 years and older (Table 2).

For newly diagnosed HD patients the prevalence of serious co-morbidity was 22%; it was 13% for patients below 60 years and 56% for patients 60 years and older ($p < 0.0001$). The prevalence of co-morbidity among patients with early-stage (Ia–IIa) was similar to that for advanced-stage (IIB–IVB) disease (data not shown).

Of the newly diagnosed NHL patients, 40% had at least one co-morbid condition: 20% of all patients younger than 60 years, 43% for patients of 60–69 years, and a steeply increasing prevalence of 61% in patients over 70 years ($p < 0.0001$). The prevalence of co-morbidity among patients with low-grade NHL was similar to that for intermediate/high-grade NHL (data not shown).

Chemotherapy was administered to 75% of patients with HD without co-morbidity versus 50% with co-morbidity ($p < 0.01$). Among elderly Hodgkin's patients with co-morbidity the proportion receiving chemotherapy was 50% lower than that for elderly patients without co-morbidity ($p < 0.01$); these differences were less pronounced for patients younger than 60 years ($p = 0.15$) (Table 3). In particular, elderly patients with early-stage HD and a co-morbid condition received chemotherapy much less often (90% versus 33%, $p = 0.05$).

Chemotherapy was administered less often to elderly patients with low-grade and intermediate/high-grade NHL ($p < 0.001$) than to younger patients, regardless of the presence of co-morbidity (Table 4). In addition to being dependent on age, the administration of chemotherapy to patients 60 years and older with intermediate/high-grade NHL further decreased in the event of co-morbidity ($p = 0.04$).

Table 3 Administration of primary chemotherapy to 194 patients with Hodgkin's disease, according to age and presence of co-morbidity

	Administration of primary chemotherapy		
	< 60 years	≥ 60 years	
Co-morbidity			
No	73%	94%	$p = 0.1$
Yes	50%	50%	$p = 0.8$
	$p = 0.15$	$p < 0.01$	

Survival within the first 4 months after diagnosis was decreased in the presence of co-morbidity in both NHL and HD for all age-groups (Table 5).

Discussion

The most common co-morbid diseases were cardiovascular diseases, COPD, and hypertension for HD patients and cardiovascular diseases, hypertension, other malignancies, and diabetes mellitus for NHL patients. More than half of all patients 60 years and older suffered from at least one co-morbid condition. Co-morbidity appeared to be more prevalent among NHL patients, presumably due to the higher mean age.

Our age-specific prevalence rates for chronic diseases did not differ markedly from 4-year prevalence data found for Dutch general practices; both increased with age [17], as was also seen in an analysis of co-morbidity among patients with breast cancer [19].

The presence of co-morbidity appeared to discourage the choice of systemic chemotherapy, especially for elderly patients; this will probably have an adverse impact on long-term survival, as was indicated by a decreased survival within 4 months after diagnosis. For elderly Hodgkin's patients, combination chemotherapy has been found to produce good results in our region [8, 21]. Since combination chemotherapy offers the best chance for cure, it is the treatment of first choice for

Table 4 Administration of primary chemotherapy to patients with NHL according to grade, age, and presence of co-morbidity

NHL grade	Administration of primary chemotherapy			
	< 60 years	60–69 years	≥ 70 years	
Low (n)	96	53	50	
Co-morbidity				
No	64%	45%	33%	p = 0.02
Yes	50%	38%	25%	p = ns
	p = ns	p = ns	p = ns	
Intermediate/high (n)	192	104	155	
Co-morbidity				
No	85%	87%	58%	p < 0.001
Yes	85%	79%	52%	p < 0.0005
	p = ns	p = ns[a]	p = ns[a]	

[a] p = 0.04 when patients 60–69 years and ≥ 70 years are grouped together.

Table 5 Overall survival (%) within the first 4 months after diagnosis in patients with NHL and HD, according to age

Co-morbidity	NHL			HD	
	< 60 years (%)	60–69 years (%)	≥ 70 years (%)	< 60 years (%)	≥ 60 years (%)
No	93	89	80	100	88
Yes	85	84	70	95	73

patients with intermediate/high-grade NHL [9]. However, elderly NHL patients reportedly receive chemotherapy less often [6]. This finding was confirmed by our study and was even independent of the presence of co-morbidity. Moreover, we found that the administration of chemotherapy is also reduced in the presence of co-morbidity, especially for elderly patients with intermediate/high-grade NHL. Obviously, the reduced administration of systemic chemotherapy is likely to influence survival adversely, especially since intermediate and high-grade lymphomas in the elderly are reported to be aggressive diseases with adverse prognostic parameters [2].

Our findings are in agreement with studies which have demonstrated that cancer patients with extensive co-morbidity are treated less aggressively than those with milder co-morbid conditions, independent of the effects of age and stage of disease [10, 19]. Moreover, a greater influence of co-morbidity than age, not only on therapeutic decision-making in lung and colorectal cancer [11, 15] but also on long-term survival of men with localized prostate cancer, has been reported [1]. This negative influence of co-morbidity on the survival of cancer patients might be due to several mechanisms: the increased risk of death due to the co-morbid condition itself, more contraindications for anticancer treatment, more indications for dose reduction, and a higher rate of treatment-related complications such as infections and cardiovascular events.

Whether the shift towards less frequent administration of chemotherapy for lymphoma patients with co-morbidity is justified or not needs to be further investigated by assessing its influence on long-term survival. Moreover, the influence of co-morbidity on staging and adherence to treatment guidelines requires elucidation.

In conclusion, co-morbidity was present in more than half of all lymphoma patients who were 60 years and older. In the presence of co-morbidity elderly lymphoma patients received chemotherapy much less often, which is likely to affect survival adversely, as was indicated by a decreased survival within 4 months after diagnosis.

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