

Comorbidity and treatment decision-making in elderly non-Hodgkin's lymphoma patients: a survey among haematologists

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ABSTRACT

Background: Elderly patients with non-Hodgkin's lymphoma (NHL) are often not treated with standard immunochemotherapy and this might have a negative impact on their survival. Little is known about the determinants that play a role in treatment decision-making of clinicians regarding elderly patients with NHL. The objective of this study was to gain more insight into these determinants.

Methods: A survey was conducted amongst haematologists in the Netherlands. The survey contained questions about comorbidity, polypharmacy, social setting, nutritional status, depression, mild cognitive impairment, dementia, activities of daily living (ADL) and instrumental activities of daily living (IADL) in relation to treatment decisions in elderly NHL patients.

Results: Of all comorbidities, respondents designated cognitive disorders and cardiovascular comorbidity as the most important factors when assessing whether an older patient with NHL is eligible for curative treatment. Also in decreasing degree of importance ADL, IADL and depressive disorder are frequently included in treatment decision-making. Almost half of the respondents feel that treatment of the elderly person is complicated as a result of a lack of scientific evidence.

Conclusion: Haematologists are aware of coexisting problems in elderly patients and they frequently take comorbidities, cognitive disorders and functional status into consideration in treatment decision-making. Future studies are needed to determine the exact role that these factors should play in the treatment of elderly patients.

Furthermore, haematologists feel that treatment of the elderly is complicated and there is a lack of scientific evidence, and therefore older adults should be better represented in clinical trials.

KEYWORDS

Comorbidity, elderly, non-Hodgkin's lymphoma, survey.

INTRODUCTION

In 2007, 1572 patients were diagnosed with aggressive non-Hodgkin's lymphoma (NHL) in the Netherlands and it is expected that the incidence will increase to almost 1900 patients in the year 2020 due to ageing of the population and increasing incidence with advancing age.¹ Currently, the median age at diagnosis is 66 years.²

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of aggressive NHL. The first choice of treatment for DLBCL is the rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) regimen. This improves complete remission rates and survival, in young as well as in elderly patients.³⁻¹² However, treatment of elderly patients with aggressive NHL can be complicated because of additional factors such as comorbidity and polypharmacy. Furthermore, elderly patients are often under-represented in clinical trials and only relatively fit elderly patients are included. Therefore

most evidence is based on a selection of patients.^{13,14} There are only a limited number of population-based studies with unselected elderly DLBCL patients. These also show that R-CHOP is associated with improved survival in comparison with other treatment strategies.^{9,12,15}

Nevertheless, elderly NHL patients are often not being treated with standard immunochemotherapy.^{5-8,10,15} Motives for suboptimal treatment are amongst others poor performance status and comorbidity, but also high age in itself is declared by physicians to be a reason for refraining from optimal treatment.^{5,8,15}

Little is known about the determinants that might play a role in the decision-making of clinicians regarding the eligibility of elderly patients with a haematological malignancy to be treated with curative intent. Therefore, we conducted a survey among haematologists in the Netherlands to gain insight into these determinants. The emphasis was on DLBCL, as this type of aggressive NHL can be treated with curative intent.

METHODS

Data collection

Haematologists were invited to complete the online questionnaire 'Treatment of the elderly with a haematological malignancy' on behalf of the Dutch-Belgian Cooperative Trial Group for Haemato-Oncology (HOVON). HOVON is a foundation that focuses on improving and promoting treatment methods for adult patients with malignant haematological disorders.¹⁶ Haematologists were invited to participate through e-mail in November 2011. Non-respondents were sent a reminder e-mail within two months.

Study measures

The questionnaire contained questions about the importance of various factors that might play a role in the decision-making of clinicians regarding treatment with curative intent in elderly patients. There were nine questions regarding the extent to which respondents agree that various comorbidities, polypharmacy, social setting and nutritional status should be taken into consideration. In addition, there were five items regarding the frequency with which depression, mild cognitive impairment, dementia, activities of daily living (ADL) and instrumental activities of daily living (IADL) are taken into account. The application of chemotherapy dose reductions in advance and refraining from curative treatment in relation to toxicity was assessed. Furthermore, the respondents were asked to what extent they feel that treatment of older adults with haematological malignancies is complicated because of a lack of scientific research and to what extent respondents exclusively treat elderly patients if they can be included in clinical trials.

Also the respondents' age and gender were assessed, as well as the type of hospital they work in. In the Netherlands, three types of hospitals can be discerned: university hospitals, tertiary medical teaching hospitals (STZ) and general hospitals. STZ hospitals are large teaching hospitals, where highly specialised care is provided.¹⁷

RESULTS

Invitations to complete the questionnaire were sent to 255 haematologists. A total of 94 questionnaires were returned (36.9% response rate), of which 87 were fully completed and seven were incomplete (*table 1*). The mean age of the respondents at the time of survey was 49.6 years. There were more male than female respondents. Of the respondents, 29.8% worked at a university hospital, 33.0% at an STZ hospital and 37.2% at a general hospital.

The two comorbidities that respondents designated as most important when assessing if an elderly patient qualifies for a curative treatment intent (answer categories totally agree and agree combined) were cognitive disorders (99%) and cardiovascular comorbidity (95.7%) (*figure 1*). These were followed by pulmonary comorbidity (88.3%), nutritional status (84.1%), social setting (79.8%), kidney disease (70.2), mobility disorders (61.7%), liver disease (57.4%), and polypharmacy (57.4%).

Respondents frequently include dementia (89%, answer categories always and often combined) and ADL (85.7%) in treatment decision-making in elderly patients with a haematological malignancy. IADL (69.4%), depressive disorder (53.2%) and mild cognitive impairment (41.3%) are less often taken into account (*figure 2*).

Twenty-three percent of the respondents often apply dose reductions in elderly patients to avoid estimated toxicity, while only 2.3% of respondents regularly refrain from treatment with curative intent for toxicity reasons (answer category 'Always' and 'Frequently' combined) (*table 2*). Of

Table 1. Sociodemographic characteristics of questionnaire respondents

	Respondents n=94 n (%)
Age at time of survey (mean ± SD) (N=65)	49.6 (9.0)
Gender	
Male	62 (66.0)
Female	32 (34.0)
Type of hospital	
University hospital	28 (29.8)
Tertiary medical teaching hospital	31 (33.0)
General hospital	35 (37.2)

Figure 1. Extent to which haematologists agree that various determinants should be included in treatment decision-making in elderly patients with a haematological malignancy

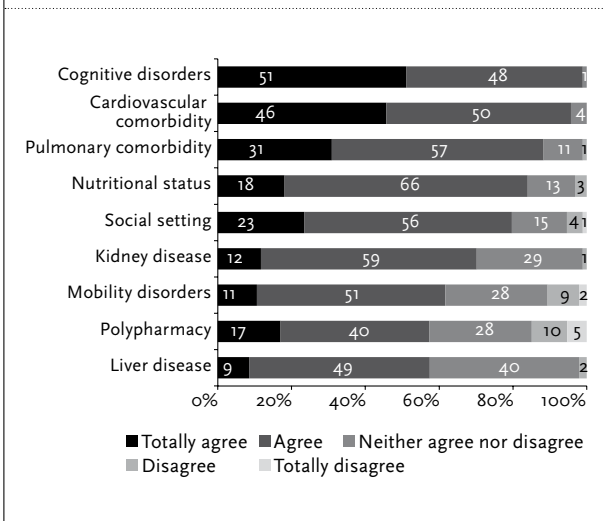
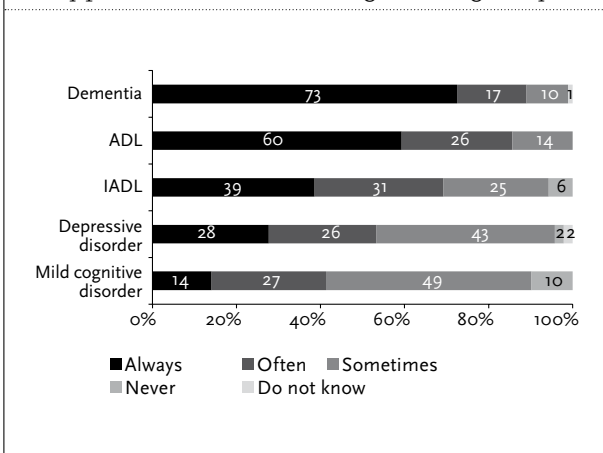


Figure 2. Frequencies with which respondents include dementia, ADL, IADL, depressive disorder and mild cognitive impairment in treatment decision-making in elderly patients with a haematological malignancy



the respondents, 45.9% feel that treatment of the elderly is often hindered because there is too little scientific evidence. A minority of respondents (10.3%) only treat elderly patients if they can be included in clinical trials.

DISCUSSION

The aim of the present study was to better understand the determinants that play a role in the decision-making of clinicians regarding treatment with curative intent of elderly patients with aggressive NHL.

Since the incidence of NHL increases with age, comorbidity is common in this patient population and the prevalence of comorbidity ranges from 35 to 79% in elderly NHL patients.¹⁸⁻²² Our study shows that haematologists are aware of this problem and that they frequently take comorbidity into consideration in treatment decisions.

We observed that, in relation to comorbidity, haematologists found cognitive disorders and cardiovascular comorbidity the most important factors in treatment decision-making. Of the cognitive disorders, in particular dementia is often included in treatment decision-making and to a lesser extent mild cognitive impairment. In addition, respondents stated that they regularly take account of ADL, IADL and depressive disorders.

Several studies demonstrate an interrelationship between the presence of comorbidity and poorer complete remission rates, progression-free survival and overall survival.^{10,18-21,23} Nevertheless, it is also observed that in the presence of comorbidity chemotherapy is less frequently applied or that the relative dose intensity is lower.^{19,20,22} This suboptimal therapy could also be an explanation for the poorer survival in the presence of comorbidity rather than comorbidity itself. On the other hand, however, there are also studies showing poorer survival in patients with comorbidity, where no relationship was found between comorbidity and chemotherapy dose reductions.^{10,21} With regard to cardiovascular comorbidity in particular, there are indications that in the presence of this the chance of

Table 2. Haematologists' responses to questions regarding dose adjustments and toxicity, lack of scientific evidence and treatment in clinical trials in elderly patients with a haematological malignancy

	Always N (%)	Frequently N (%)	Sometimes N (%)	Never N (%)	Do not know N (%)
I apply dose reductions in advance in elderly patients because of expected toxicity	4 (4.6)	16 (18.4)	51 (58.6)	16 (18.4)	0 (0.0)
I refrain from curative treatment in elderly patients because of expected toxicity	0 (0.0)	2 (2.3)	69 (79.3)	16 (18.4)	0 (0.0)
I feel treatment decision-making in elderly patients is complicated because there is a lack of scientific evidence	7 (8.0)	33 (37.9)	36 (41.4)	11 (12.6)	0 (0.0)
I treat elderly patients exclusively in clinical trials	0 (0.0)	9 (10.3)	51 (58.6)	20 (23.0)	7 (8.0)

being treated with chemotherapy is reduced and the risk of toxicity is increased.²¹ And lastly, in various studies a relation was observed between survival and nutritional status, cognition, frailty, IADL, ADL and depression, but this could not be confirmed in other studies.²³⁻²⁸ As a result of these inconsistent study results, the interpretation of coexisting diseases in elderly patients with regard to treatment consequences is complicated and more research in this field is necessary.

Interestingly, respondents state that they regularly take comorbidities, cognitive disorders, the patients' social setting, nutritional status, ADL, IADL and depression into consideration when making treatment decisions. However, in daily clinical practice systematic assessments are rarely carried out to identify problems in these areas; this is, among other reasons, because it is time consuming. In general, the physicians' judgment is used to estimate whether there are additional problems, even though it is known that this is not very reliable. Comprehensive assessment results in the detection of a higher number of previously unknown geriatric problems than the physicians' judgment, although it is still not known how to adjust treatment decisions based on comprehensive geriatric assessments.²⁹⁻³³

Finally, a large proportion of the respondents feel that treatment of the elderly is difficult, because relatively little scientific research has been done among this population. Indeed, older adults are poorly represented in clinical trials, due to direct age-based exclusion as well as due to restrictive inclusion criteria, selecting for the fittest elderly.^{13,14} Since the majority of all DLBCL patients are elderly, it is important that they are better represented in randomised controlled trials so that treatment of this population can be improved.

The current study has some limitations. We did not define the term 'elderly patient', but left this to the interpretation of the respondent. Furthermore, we cannot exclude that haematologists with a special interest for elderly patients with NHL responded. However, there are no direct indications for this.

The strengths of our study are that this is, to the best of our knowledge, the first study investigating the determinants that influence treatment decision-making. In addition, it is a multicentre study including haematologists from university hospitals as well as STZ hospitals and general hospitals and the participation rate of the haematologists was high. Therefore we are confident that the results of our study are generalisable.

In conclusion, haematologists are well aware of coexisting problems in elderly patients and comorbidities, cognitive disorders and functional status are frequently included in treatment decisions. There is, however, no convincing evidence of the exact role comorbidity should play in the treatment of elderly NHL patients. Moreover, clinicians

feel that treatment is complicated due to a lack of scientific evidence. Therefore, future studies should address this problem and older adults should be better represented in clinical trials, so that evidence-based guidelines for the treatment of elderly patients with a haematological malignancy can be developed.

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DISCLOSURES

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REFERENCES

1. KWF kankerbestrijding SK. Kanker in Nederland tot 2020. Trends and Prognoses (in Dutch). <http://www.kwfkankerbestrijding.nl>. September 2011.
2. <http://www.seer.cancer.gov>. (Accessed August 23, 2013).
3. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *New Engl J Med*. 2002;346:235-42.
4. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 2005;23:4117-26.
5. van de Schans SA, Wymenga AN, van Spronsen DJ, Schouten HC, Coebergh JW, Janssen-Heijnen ML. Two sides of the medallion: poor treatment tolerance but better survival by standard chemotherapy in elderly patients with advanced-stage diffuse large B-cell lymphoma. *Ann Oncol*. 2012;23:1280-6.
6. Peters FP, Lalisang RI, Fickers MM, et al. Treatment of elderly patients with intermediate- and high-grade non-Hodgkin's lymphoma: a retrospective population-based study. *Ann Hematol*. 2001;80:155-9.
7. Thieblemont C, Grosseuvre A, Houot R, et al. Non-Hodgkin's lymphoma in very elderly patients over 80 years. A descriptive analysis of clinical presentation and outcome. *Ann Oncol*. 2008;19:774-9.
8. Peters FP, Fickers MM, Erdkamp FL, Wals J, Wils JA, Schouten HC. The effect of optimal treatment on elderly patients with aggressive non-Hodgkin's lymphoma: more patients treated with unaffected response rates. *Ann Hematol*. 2001;80:406-10.
9. Lee L, Crump M, Khor S, et al. Impact of rituximab on treatment outcomes of patients with diffuse large b-cell lymphoma: a population-based analysis. *Br J Haematol*. 2012;158:481-8.
10. Lin TL, Kuo MC, Shih LY, et al. The impact of age, Charlson comorbidity index, and performance status on treatment of elderly patients with diffuse large B cell lymphoma. *Ann Hematol*. 2012;91:1383-91.

11. Griffiths RI, Gleeson ML, Mikhael J, Dreyling MH, Danese MD. Comparative effectiveness and cost of adding rituximab to first-line chemotherapy for elderly patients diagnosed with diffuse large B-cell lymphoma. *Cancer*. 2012;118:6079-88.
12. Boslooper K, Kibbelaar R, Storm H, et al. Treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone is beneficial but toxic in very elderly patients with diffuse large B-cell lymphoma: a population-based cohort study on treatment, toxicity and outcome. *Leuk Lymphoma*. 2013;Jul 29. [Epub ahead of print].
13. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol*. 2004;22:4626-31.
14. Bellera C, Praud D, Petit-Moneger A, McKelvie-Sebileau P, Soubeyran P, Mathoulin-Pelissier S. Barriers to inclusion of older adults in randomised controlled clinical trials on Non-Hodgkin's lymphoma: A systematic review. *Cancer Treat Rev*. 2013;39:812-7.
15. Varga C, Holcroft C, Kezouh A, et al. Comparison of outcomes among patients aged 80 and over and younger patients with diffuse large B cell lymphoma: a population based study. *Leuk Lymphoma*. 2013.
16. <http://www.hovon.nl>. (Accessed August 22, 2013).
17. <http://www.stz.nl>. (Accessed August 22, 2013).
18. van Spronsen DJ, Janssen-Heijnen ML, Breed WP, Coebergh JW. Prevalence of co-morbidity and its relationship to treatment among unselected patients with Hodgkin's disease and non-Hodgkin's lymphoma, 1993-1996. *Ann Hematol*. 1999;78:315-9.
19. van Spronsen DJ, Janssen-Heijnen ML, Lemmens VE, Peters WG, Coebergh JW. Independent prognostic effect of co-morbidity in lymphoma patients: results of the population-based Eindhoven Cancer Registry. *Eur J Cancer*. 2005;41:1051-7.
20. Kobayashi Y, Miura K, Hojo A, et al. Charlson Comorbidity Index is an independent prognostic factor among elderly patients with diffuse large B-cell lymphoma. *J Cancer Res Clin Oncol*. 2011;137:1079-84.
21. Janssen-Heijnen ML, van Spronsen DJ, Lemmens VE, Houterman S, Verheij KD, Coebergh JW. A population-based study of severity of comorbidity among patients with non-Hodgkin's lymphoma: prognostic impact independent of International Prognostic Index. *Br J Haematol*. 2005;129:597-606.
22. Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. *Crit Rev Oncol Hematol*. 2005;55:231-40.
23. Winkelmann N, Petersen I, Kiehnopf M, Fricke HJ, Hochhaus A, Wedding U. Results of comprehensive geriatric assessment effect survival in patients with malignant lymphoma. *J Cancer Res Clin Oncol*. 2011;137:733-8.
24. Spina M, Balzarotti M, Uziel L, et al. Modulated chemotherapy according to modified comprehensive geriatric assessment in 100 consecutive elderly patients with diffuse large B-cell lymphoma. *Oncologist*. 2012;17:838-46.
25. Nabhan C, Smith SM, Helenowski I, et al. Analysis of very elderly (>=80 years) non-hodgkin lymphoma: impact of functional status and co-morbidities on outcome. *Br J Haematol*. 2012;156:196-204.
26. Soubeyran P, Fonck M, Blanc-Bisson C, et al. Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. *J Clin Oncol*. 2012;30:1829-34.
27. Aaldriks AA, Maartense E, le Cessie S, et al. Predictive value of geriatric assessment for patients older than 70 years, treated with chemotherapy. *Crit Rev Oncol Hematol*. 2011;79:205-12.
28. Mols F, Husson O, Roukema JA, van de Poll-Franse LV. Depressive symptoms are a risk factor for all-cause mortality: results from a prospective population-based study among 3,080 cancer survivors from the PROFILES registry. *J Cancer Surviv*. 2013;7:484-92.
29. Wedding U, Koding D, Pientka L, Steinmetz HT, Schmitz S. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. *Crit Rev Oncol Hematol*. 2007;64:1-9.
30. Tucci A, Ferrari S, Bottelli C, Borlenghi E, Drera M, Rossi G. A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. *Cancer*. 2009;115:4547-53.
31. Kenis C, Bron D, Libert Y, et al. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. *Ann Oncol*. 2013;24:1306-12.
32. Horgan AM, Leighl NB, Coate L, et al. Impact and feasibility of a comprehensive geriatric assessment in the oncology setting: a pilot study. *Am J Clin Oncol*. 2012;35:322-8.
33. Girre V, Falcou MC, Gisselbrecht M, et al. Does a geriatric oncology consultation modify the cancer treatment plan for elderly patients? *J Gerontol A Biol Sci Med Sci*. 2008;63:724-30.