Identification of clinical parameters predictive of one-year survival using two geriatric tools in *clinically fit* older patients with haematological malignancies: major impact of cognition

S. Dubruille M.A[1-2], Y. Libert Ph.D[1], M.Roos[3], S.Vandenbossche M.A[1], A. Collard[3], N. Meuleman M.D, Ph.D[4], M. Maerevoet M.D[4], A-M Etienne Ph.D[5], C. Reynaert M.D, Ph.D[2], D. Razavi M.D, Ph.D[1], D. Bron M.D, Ph.D[4]

1: Clinic of Psycho-Oncology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
2: Université Catholique de Louvain, Service de Médecine Psychosomatique, Cliniques Universitaires de Mont-Godinne, Belgium
3: Oncogeriatry Unit, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
4: Department of Hematology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
5: Université de Liège, Faculté des Sciences psychologiques et de l'Education, Liège, Belgium

ABSTRACT

Little is known about the reliability of G8 screening tool and the prognostic value of clinical parameters within the Comprehensive Geriatric Assessment (CGA) in *clinically fit* older patients with haematological malignancies. This study was performed to assess the reliability of G8 as a screening tool and to determine the predictive value of CGA items in terms of one-year overall survival (OS). G8 and CGA were proposed to 107 consecutive patients (65-89yrs) with haematological malignancies that were judged clinically fit to receive chemotherapy. Ninety patients were evaluable with both scales; 72% and 80% were defined as “vulnerable” when evaluated with G8 (≤14.5) or CGA (≥2 impairments) respectively. The area under ROC-curve of G8 compared to CGA was 0.749 ± 0.051. Neither G8 nor CGA total score were predictive of one-year OS. However, age (HR=1.09, 95%CI: 1.009-1.185; p=0.029), diagnosis (HR=5.99, 95%CI: 2.322-15.428; p<0.001) and cognitive status (HR=3.50, 95%CI: 1.132-10.849; p=0.030) were predictive of OS. We conclude that in our selected haematological patients 1) the G8 score does not help selecting patients for CGA 2) the G8 and CGA total score do not predict OS 3) in addition to the age and disease itself, cognitive impairment appears to be a powerful prognostic factor.

Keywords: Geriatric assessment, elderly, haematological malignancy, cognitive impairment

INTRODUCTION

Growing evidence suggests that a Comprehensive Geriatric Assessment (CGA) in older patients with malignant haemopathies helps haematologists to detect “frailty” in cancer patients leading to useful interventions but less useful to identify patients for whom chemotherapy should be avoided or reduced as it could negatively impact functionality, quality of life, treatment-related toxicity or survival (1, 2). However, the CGA is time consuming, expensive, complex, not reproducible and not helpful for an individual patient with a specific treatment (3).

To overcome these difficulties, the G8 screening test was developed by Soubeyran and colleagues (4) to identify vulnerable patients who might benefit from a full CGA and adapted interventions. In a systematic review of a mixed population of oncological patients, G8 showed a good sensitivity in detecting geriatric impairments in multiple domains, in fact, most of these patients were identified as having geriatric impairments (5). However, some concerns were raised regarding the G8’s specificity, as many patients with no geriatric impairment were incorrectly identified as requiring further assessment.

Today, most of the studies on the G8 screening tool have focused either exclusively on patients with solid tumors or on a mixed population composed of a minority with haematological malignancies. Only one study has focused on a heterogeneous population of patients with haematological malignancies (6). Nevertheless, specific data are lacking on the use of G8 for specific older patients with haematological malignancies judged *clinically fit* by their physicians to receive chemotherapy and the

use of the G8 screening tool for those patients remains to be validated in a large cohort.

“Fitness scoring” is particularly important in the setting of malignant hemopathies because most of these diseases are observed in adults above the age of 65 years (7). Additionally, compared to solid tumors, hemopathies can be curable diseases – even in older patients– and it’s crucial to identify this curable population. Finally, in haemato-oncology, although “frail” (patients with geriatric syndrome) older patients are easily detected by physicians and managed in palliative units, *clinically fit* older patients are regularly over- or undertreated solely based on their age. Consequently, detecting the margin between “fit” (patients with a PS <2 and full functional autonomy) and “vulnerable” (patients who do not meet the criteria for “fit” or “frail”) patients is crucial because of the risks entailed by an inadequate therapeutical approach. On one hand, undertreating a patient because of comorbidities – although these could be reversible if due to the disease itself – could prevent this patient from being cured. On the other hand, treating undetected “vulnerable” patients with a standard chemotherapy regimen could result in severe side effects ultimately leading to geriatric syndromes, dependence of the patient, and sometimes, life-threatening adverse events.

The objectives of this study were thus a) to assess the reliability of the G8 screening tool compared to a full CGA in *clinically fit* older patients with haematological malignancies b) to further investigate the predictive value of G8 and different CGA items in terms of one-year OS.

METHODS

Patient's population

This prospective longitudinal study was conducted in the haematology department of a Belgian cancer center after approval from a national Review Board. All consecutive volunteer inpatients, fulfilling the inclusion criteria were invited to participate and provided written informed consent. To fulfill the inclusion criteria, the patients suffering from haematological cancer had to be at least 65 years old, were informed about the diagnosis of malignant haemopathies, hospitalized for chemotherapy after their physician's clinical judgment, and able to speak French. Patients were excluded if they were hospitalized in a palliative care unit, if they had geriatric syndromes such as dementia or were unable to achieve the assessment for physical or psychological reasons. Patients were screened in the first 48 hours after admission.

Assessment procedure

The complete assessment lasted approximately one hour and was assisted by an independent investigator. All patients were invited to complete the G8 screening test (4) and a full Comprehensive Geriatric Assessment (CGA). The CGA in this study included demographic data and 8 domains related to functional status (Activities of Daily Living (ADL) (8) and Instrumental Activities of Daily Living (IADL) (9)) risk of falls status (Time up and Go test (TUG) (10) and fall history during the last year (11)), fatigue status (Mobility-tiredness scale (Mob-T) (12)), nutritional status (Mini Nutritional Assessment (MNA) (13), cognitive status (Mini Mental State Examination (MMSE) (14) and Montreal Cognitive Assessment (MoCA) (15)), emotional status (Hospital Anxiety and Depression Scale (HADS) (16) and Geriatric Depression Scale (GDS-4) (17)), polypharmacy (18) and comorbidities (Charlson Comorbidity Scale

(CCI) (19)). Each test was scored on a dichotomous scale, based on individual cut-off points reported in the literature. Patients exhibiting deficiencies in one of the tests within each domain were defined as impaired in this domain. In accordance with previous research, patients exhibiting impairments in two or more domains within the CGA were defined as vulnerable (20, 21). In addition, ECOG performance status (22) was recorded and diagnosis, initial treatment choice (full dose or reduced-dose chemotherapy) based on a multidisciplinary team decision, intolerance to treatment, death and cause of death were extracted from medical records.

Statistical analyses

Descriptive analysis was used to describe the participants' baseline characteristics. To obtain the discriminatory power of the G8 (test instrument) for identifying ≥ two geriatric abnormalities on the CGA (gold standard instrument), using estimated area under the ROC curve on the hypothesis of equality with 0.5 and with 95% confidence interval as an index of predictive accuracy. Sensitivity (S) and specificity (Sp) with 95% confidence intervals of G8 test was calculated at the cut-off score, in comparison with the gold standard, and in comparison with each of the domains within of the CGA. Kaplan-Meir survival curves were generated and groups were compared using the log-rank test. Each CGA variable associated with OS ($P<0.1$) was evaluated with a multivariate Cox proportional hazards model adjusting for age, gender, diagnosis, initial treatment choice and tolerance to treatment; adjusted hazard ratios (HR), 95% confidence intervals (95%CI), and p-values are reported.

RESULTS

Patients' population

Among the 107 eligible inpatients, 15 refused to take part in the study and 2 completed only one screening tool, leaving 90 assessable patients, with a median age of 74 (65-89 years old). Table 1 shows sociodemographic details and medical characteristics of these patients. Fifty four percent of the patients could be classified as "younger", aged between 65 and 74 years. Most patients had a favorable prognosis (85%) and the majority of these patients received a full dose of chemotherapy (66%). Only 33% of the older patients were intolerant to the treatment.

Vulnerability, G8 and CGA

Table 2 shows vulnerability of these patients in different geriatric scale. Seventy-two percent of the patients presented a G8 score ≥14.5 points (vulnerable). The median score achieved on the G8 scale was 12.5 (range 5-17). CGA identified 80% (n=72) of the patients as vulnerable (≥ 2 impairments). The most frequent deficit was observed in the evaluation of comorbidities (61%). Problems in functional status (ADL, IADL) occurred in 11% and 37% (28% of men and 49% of women) of the patients respectively. Signs of emotional difficulties (HADS) were detected among 16% of the patients. Cognitive impairment was detected among 31 % of the patients with the MMSE (<27) and among 51% with the MoCA (<26).

Reliability, G8 and CGA

Fig 1. shows the receiver operating characteristics (ROC) analysis of the G8 compared to the CGA as the gold standard among these patients. The area under

the ROC-curve (AUC ± SE) of the G8 was 0.749 ± 0.051. A sensitivity of 79.2% and a specificity of 55.6% for G8 (cut-off score ≤ 14.5) were obtained. An optimal cut-off score of 13.5 was found for the G8 tool, with a sensitivity of 61.1% (95% CI [49.5-71.5]) and a specificity of 72.2% (95% CI [48.7-87.6]). The analysis of the AUC values of the screening instruments versus the different items within the CGA showed that the G8 identified nutritional difficulties (MNA; 0.887 ± 0.019) and locomotion difficulties (TUG; 0,874 ± 0,094) with good diagnostic accuracy; loss of autonomy (ADL; 0,756 ± 0.079), fatigue (Mob-t; 0,716 ± 0,046) and emotional difficulties (HADS; 0,798 ± 0,077) with moderate diagnostic accuracy, and fall during the last year (falls; 0,526 ± 0,075), cognitive impairment (MMSE; 0,623 ± 0,178 and MoCA; 0,669 ± 0,055), polypharmacy (number of drugs; 0,533 ± 0,048) and comorbidities (CCI; 0,486 ± 0,047) with poor diagnostic accuracy.

Survival, G8 and CGA

Table 3 shows the univariate association between one-year overall survival and the baseline and geriatric characteristics. During the first year of follow-up, 28% (n=25) of older patients with haematological malignancies died. The leading cause of death (84%) was disease progression. Only four older patients died due to treatment related toxicity. Using the unadjusted effects of routine parameters and CGA parameters, we found that the G8 impairments had no impact on one-year OS (p=0.988). Surprisingly, the impairment in the CGA total score also did not impact the one-year OS (p=0.999). Only age ≥ 75 years (p=0.010), unfavorable prognosis (p<0.001) and cognitive impairment measured by the MMSE and/or the MoCA (p=0.013) influenced the OS. After adjusting for routine clinical parameters, as shows

in table 4, cognitive impairment (p=0.030) remained significantly associated with worse OS. Fig 2. shows the Kaplan-Meier overall survival between patients without cognitive impairment (MMSE ≥27 and MoCA ≥26) and patients with cognitive impairment (MMSE<27 or MoCA <26) in one-year overall survival. This figure demonstrated that patients with cognitive impairment had a higher mortality risk (p=0.013).

DISCUSSION

The aims of this study were to evaluate in consecutive *clinically fit* older patients with haematological malignancies the reliability of the G8 screening tool compared to a full CGA and to identify the predictive value of clinical CGA parameters in terms of one-year OS.

First, it should be emphasized that our screening was performed in a population admitted for chemotherapy according to clinical physician's judgment about the tolerance of the patients. This prospective study showed that, at the start of their treatment, 72% of *clinically fit* older patients with haematological malignancies were defined as vulnerable by the G8 and 80% when evaluated with the CGA (≥ two CGA abnormalities). This high prevalence of vulnerability confirms the findings from Soubeyran et al. (23) who reported 80% of vulnerable patients in their unselected oncology population, but with a less stringent definition of impairment (≥ one CGA abnormality). One could even question the need for a screening instrument in a haematological population, given such a high prevalence of vulnerability.

As for the G8 screening tool, we found that it identified vulnerability in *clinically fit* older patients with haematological malignancies with moderate diagnostic accuracy. This differs from other studies which demonstrated that the G8 had a good diagnostic accuracy for identifying patients who might benefit from additional investigations (23). This discrepancy may be explained by the fact that these studies focused either exclusively on solid tumors, or on a mixed population with a minority of haematological malignancies, and that the G8 screening tool was initially validated in

a large French oncogeriatric population (23). In this large oncologic population, the sensitivity (S) of the G8 was 76.6% and the specificity (Sp) was 64.4%. In our study, the G8 had similar S (79.2%) but a poorer Sp (55.6%) with a cut-off score of 14.5. This lower specificity may be explained by the high incidence of fatigue and nutritional problems, common in haematological patients. This is in accordance with our results that demonstrated that the G8 was well correlated with the nutritional domain of the CGA and poorly correlated with other domains, confirming its primarily function-based content. However, in many haematological patients, these nutritional problems are due to the disease itself and are often reversible with adequate management. This is a major issue to take into account when making therapeutical decisions in order to avoid under-treatment of older patients that adequate chemotherapy could possibly cure or significantly prolong their survival. We found that a better cut-off score for the G8 in this study was 13.5, yielding a moderate sensitivity of 61.1% and a moderate specificity of 72.2%. However, in haematological patients, when curable intent is possible, it is important that screening tools have a good specificity in order to avoid under-treatment but also a good sensitivity to avoid over-treatment of true “vulnerable” patients that could develop severe side effects, ultimately leading to geriatric syndromes and loss of autonomy. It seems, however, that in its current form, the G8 is not adapted to our haematological population as a screening tool to optimize treatment. In other words, the G8 screening tool does not improve patients’ health-related quality of life through adapted care and does not adequately select patients susceptible to tolerate optimal treatment. These results are very similar to those observed by Hamaker et al. (6) in a recent paper of older patients with haematological malignancies, demonstrating that using the G8 in a two-stepped approach to the geriatric assessment did not appear beneficial.

In a second part of this study, we focused essentially on the prediction of survival in our selected population. Surprisingly, neither the G8 nor the CGA total score appeared to predict one-year survival. This conclusion is in contradiction with the results reported by Kenis (24) and Hamaker (6) who found a significant association of impaired G8 with poor prognosis in a mixed population of older cancer patients (24) and in older patients with malignant haemopathies (6). Our discrepancy with this last paper can be explained by the fact that in our population, 85% of the patients had a favorable prognosis compared with 42% in Hamaker's study, and the large majority of our patients were alive after a one-year follow-up (72%). In addition, we selected a population of *clinically fit* older patients admitted to receive chemotherapy. It is important to remember that, initially, the G8 screening tool was built only to predict the need for full CGA in older patients (23). The poor prognostic value of the CGA total score in our population can be explained by the fact that – in malignant haemopathies – other important prognostic factors related to the disease itself such as anemia (25), albumin level (26) or poor cytogenetics (27), which were not assessed in this study, have a more prominent influence on survival.

A multivariable analysis was performed on the different items of the CGA and surprisingly, only cognitive status in the CGA had a predictive value for one-year OS. This result is concordant with other studies that have demonstrated that older cancer patients with cognitive impairment have a higher risk of death compared to those with normal cognitive function (28-30). These results can be easily explained. First, older patients with cognitive impairment are less compliant to the treatment (31). Second, cognitive impairment in older patients are often associated with late-life depression (32) which is correlated with a poorer survival in older cancer patients (33). Third,

older people with cognitive impairment are more frequently isolated (34), and turn away persons who want to help, to avoid facing their difficulties (35). Finally, it is increasingly reported that chemotherapeutic agents can worsen the patient's cognitive status (36-38). Thus, it is obvious those patients with cognitive impairment at the start of chemotherapy are more vulnerable, and that their vulnerability can be worsened by chemotherapeutic agents (39, 40).

Although our patient population size is somewhat too small to draw definite conclusions, as many patients with haematological malignancies die from their disease and rarely from comorbidities (39), our study suggests that all *clinically fit* patients without cognitive impairment could benefit from full dose chemotherapy and should thus be appropriately screened for such impairment. This assumption needs further investigation, but could be highly relevant for future treatment guidelines. Patients with cognitive impairment should definitely be identified and steered towards rehabilitation and adapted care (38), including psychological support (35). More generally, health services should be adapted to the needs of this vulnerable population (need for services to be organized at the bedside and flexibility in scheduling appointments).

Finally, although the CGA is considered as the gold standard to improve the management of older patients, its content is still debated. Additionally, an excess of tools and cut-off scores identifying impairment in geriatric domains are found in the literature. In our study, we focused on two validated scales of cognitive and emotional status, i.e. MMSE and MoCA for cognitive status, while the MoCA is more sensitive to detect mild cognitive impairment that which explains the greater

percentage of cognitive impairment measured by this scale. We chose the CCI to evaluate the number of co-morbidities but their severity is probably more important than their quantity since an accumulation of co-morbidities was not found to be a good predictor of the patient's tolerance to chemotherapy (40, 41). In agreement with this assumption, the CIRS-G could be a more appropriate scale. The predictive relevance of our screening tools in terms of toxicity could not be evaluated in this study since the number of toxic deaths was very low in our series of *clinically fit* older haematological patients. Finally, malignant haemopathies are heterogeneous and the risk profile associated with non-aggressive lymphomas is substantially different from that of acute myeloid leukaemia's (AML), and the disease itself has a major impact on survival when a multivariate analysis is performed.

To our knowledge, this is the first prospective study investigating the reliability of the G8 to identify *clinically fit* patients who should benefit from a CGA, and evaluating the prognostic value of clinical parameters within the CGA. Our study showed that 1) G8 score does not help selecting patients for full CGA 2) the G8 and CGA total score do not predict OS 3) in addition to age and the disease itself, cognitive impairment appears to be a powerful prognostic factor. Prospective trials are now required to further determine whether better identification and management of cognitive impairment in clinically fit older patients could improve survival.

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Disclosure

The author(s) indicated no conflicts of interest.

Author Contributions

Study concept and design: D. Bron, Y. Libert, D. Razavi

Data acquisition: S. Dubruille, M. Roos, S. Vandenbossche, A. Collard, M. Maerevoet

Quality control of data and algorithms: S. Dubruille, M. Roos, S. Vandenbossche, A. Collard, M. Maerevoet

Data analysis and interpretation: S. Dubruille, Y. Libert, D. Bron

Statistical analysis: S. Dubruille

Manuscript preparation: S. Dubruille

Manuscript editing: S. Dubruille, Y. Libert, D. Bron

Manuscript review: D. Bron, Y. Libert, D. Razavi, N. Meuleman, M. Maerevoet, C. Reynaert, A-M Etienne, S. Dubruille

Obtained funding: C. Reynaert, D. Bron, D. Razavi, Y.Libert, A-M Etienne

REFERENCES

1. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, Lichtman S, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Critical reviews in oncology/hematology. 2005 Sep;55(3):241-52.
2. Hamaker ME, Prins MC, Stauder R. The relevance of a geriatric assessment for elderly patients with a haematological malignancy--a systematic review. Leukemia research. 2014 Mar;38(3):275-83.
3. Extermann M, Meyer J, McGinnis M, Crocker TT, Corcoran MB, Yoder J, et al. A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. Critical reviews in oncology/hematology. 2004 Jan;49(1):69-75.
4. Soubeyran PB GC, Blanc F, Ceccaldi J, Blanc-Blisson J, Mertens C, et al. . Validation of a screening test for elderly patients in oncology. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(abstr 20568).
5. Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. The Lancet Oncology. 2012 Oct;13(10):e437-44.
6. Hamaker ME, Mitrovic M, Stauder R. The G8 screening tool detects relevant geriatric impairments and predicts survival in elderly patients with a haematological malignancy. Annals of hematology. 2014 Jun;93(6):1031-40.
7. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood. 2006 Jan 1;107(1):265-76.
8. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. The Gerontologist. 1970 Spring;10(1):20-30.
9. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. The Gerontologist. 1969 Autumn;9(3):179-86.
10. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. Journal of the American Geriatrics Society. 1991 Feb;39(2):142-8.
11. Lamb SE, Jorstad-Stein EC, Hauer K, Becker C, Prevention of Falls Network E, Outcomes Consensus G. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. Journal of the American Geriatrics Society. 2005 Sep;53(9):1618-22.
12. Fieo RA, Mortensen EL, Rantanen T, Avlund K. Improving a measure of mobility-related fatigue (the mobility-tiredness scale) by establishing item intensity. Journal of the American Geriatrics Society. 2013 Mar;61(3):429-33.
13. Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. Nutrition reviews. 1996 Jan;54(1 Pt 2):S59-65.
14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research. 1975 Nov;12(3):189-98.
15. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society. 2005 Apr;53(4):695-9.
16. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica Scandinavica. 1983 Jun;67(6):361-70.

17. Sheikh JI YJ. Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. New-york: The Haworth Press, 1986.
18. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. Journal of clinical epidemiology. 2012 Sep;65(9):989-95.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases. 1987;40(5):373-83.
20. Mohile SG, Bylow K, Dale W, Dignam J, Martin K, Petrylak DP, et al. A pilot study of the vulnerable elders survey-13 compared with the comprehensive geriatric assessment for identifying disability in older patients with prostate cancer who receive androgen ablation. Cancer. 2007 Feb 15;109(4):802-10.
21. Kellen E, Bulens P, Deckx L, Schouten H, Van Dijk M, Verdonck I, et al. Identifying an accurate pre-screening tool in geriatric oncology. Critical reviews in oncology/hematology. 2010 Sep;75(3):243-8.
22. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American journal of clinical oncology. 1982 Dec;5(6):649-55.
23. Soubeyran P BC, Goyard J, Heitz D, Cure H, Rousselot H, et al. . Validation of the G8 screening tool in geriatric oncology: the ONCODAGE project. . Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(suppl; abstr 9001).
24. Kenis C, Decoster L, Van Puyvelde K, De Greve J, Conings G, Milisen K, et al. Performance of two geriatric screening tools in older patients with cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014 Jan 1;32(1):19-26.
25. Stauder R, Thein SL. Anemia in the elderly: clinical implications and new therapeutic concepts. Haematologica. 2014 Jul;99(7):1127-30.
26. Peyrade F, Jardin F, Thieblemont C, Thyss A, Emile JF, Castaigne S, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. The Lancet Oncology. 2011 May;12(5):460-8.
27. Schoch C, Kern W, Schnittger S, Buchner T, Hiddemann W, Haferlach T. The influence of age on prognosis of de novo acute myeloid leukemia differs according to cytogenetic subgroups. Haematologica. 2004 Sep;89(9):1082-90.
28. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der Sangen MJ, Nieuwenhuijzen GA, et al. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. European journal of cancer. 2005 Mar;41(5):779-85.
29. Robb C, Boulware D, Overcash J, Extermann M. Patterns of care and survival in cancer patients with cognitive impairment. Critical reviews in oncology/hematology. 2010 Jun;74(3):218-24.
30. Klepin HD, Geiger AM, Tooze JA, Kritchevsky SB, Williamson JD, Pardee TS, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. Blood. 2013 May 23;121(21):4287-94.
31. Granjon C BM, Frederico D, Blanc P, Gonthier R. Is there a risk of drug accidents in elderly subjects with cognitive disorders? A study of 82 demented institutionalized patients. NPG. 2006;6(35):21-8.

32. Li W, Muftuler LT, Chen G, Ward BD, Budde MD, Jones JL, et al. Effects of the coexistence of late-life depression and mild cognitive impairment on white matter microstructure. Journal of the neurological sciences. 2014 Mar 15;338(1-2):46-56.
33. Wagner DC, Short JL. Longitudinal predictors of self-rated health and mortality in older adults. Preventing chronic disease. 2014;11:E93.
34. Amieva H, Stoykova R, Matharan F, Helmer C, Antonucci TC, Dartigues JF. What aspects of social network are protective for dementia? Not the quantity but the quality of social interactions is protective up to 15 years later. Psychosomatic medicine. 2010 Nov;72(9):905-11.
35. Dubruille S, Libert Y, Merckaert I, Reynaert C, Vandenbossche S, Roos M, et al. The prevalence and implications of elderly inpatients' desire for a formal psychological help at the start of cancer treatment. Psycho-oncology. 2014 Jul 31.
36. Schagen SB, van Dam FS, Muller MJ, Boogerd W, Lindeboom J, Bruning PF. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. Cancer. 1999 Feb 1;85(3):640-50.
37. Hurria A, Goldfarb S, Rosen C, Holland J, Zuckerman E, Lachs MS, et al. Effect of adjuvant breast cancer chemotherapy on cognitive function from the older patient's perspective. Breast cancer research and treatment. 2006 Aug;98(3):343-8.
38. Mandelblatt JS, Stern RA, Luta G, McGuckin M, Clapp JD, Hurria A, et al. Cognitive impairment in older patients with breast cancer before systemic therapy: is there an interaction between cancer and comorbidity? Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014 Jun 20;32(18):1909-18.
39. Kendal WS. Dying with cancer: the influence of age, comorbidity, and cancer site. Cancer. 2008 Mar 15;112(6):1354-62.
40. Maas HA, Janssen-Heijnen ML, Olde Rikkert MG, Machteld Wymenga AN. Comprehensive geriatric assessment and its clinical impact in oncology. European journal of cancer. 2007 Oct;43(15):2161-9.
41. Lazarovici C KR, Leignel D, Fabre-Guillevin E, Minard A, Gisselbrecht M. Factors leading oncologists to refer elderly cancer patients for geriatric assessment. J Geriatr Oncol. 2011;2:194-9.