Chapter

Predictive value of geriatric assessment for patients older than 70 years, treated with chemotherapy

A.A. Aaldriks, E. Maartense, S. le Cessie, E.J. Giltay, H.A. Verlaan, L.G.M. van der Geest,
W.M. Kloosterman-Boele, M.T. Peters-Dijkshoorn, B.A. Blansjaar, H.W. van Schaick, J.W.R. Nortier

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Abstract

Introduction. Comprehensive geriatric assessment (CGA) gives useful information on the functional status of older cancer patients. However, its meaning for a proper selection of elderly patients before chemotherapy and, even more important, the influence of chemotherapy on the outcome of geriatric assessment is unknown.

Methods. 202 cancer patients, for whom an indication for chemotherapy was made by the medical oncologist, underwent a GA before start of chemotherapy by Mini Nutritional Assessment (MNA), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Groningen Frailty Index (GFI) and Mini Mental State Examination (MMSE). After completion of a minimum of four cycles of chemotherapy or at six months after the start of chemotherapy the GFI and MMSE assessment was repeated.

Results. Frailty was shown in 10% of patients by means of MMSE, 32% by MNA, 37% by GFI and in 15% by IQ-CODE. Compared to patients who received 4 or more cycles of chemotherapy, the MNA and MMSE scores were significantly lower for patients treated with less than 4 cycles (p=0.001 and p=0.04 respectively). The mortality rate after start of chemotherapy was increased for patients with low MNA and high GFI scores with hazard ratios of 2.19 (95% confidence interval [CI]: 1.42-3.39; p<0.001) and 1.80 (95% CI: 1.17-2.78; p=0.007), respectively. After adjusting for sex, age, purpose of chemotherapy and type of malignancy these hazard ratios remained significant (p<0.001 and p= 0.004), respectively. Finally, for the 51 patients who underwent repeated post-chemotherapy evaluation by GFI and MMSE, a statistically significant deterioration for the MMSE (p=0.041) was found but not for the GFI.

Conclusions. Both inferior MNA and MMSE scores increased the probability not to complete chemotherapy. Also, an inferior score for MNA and GFI showed an increased mortality risk after the start of chemotherapy. The mean MMSE score worsened significantly during chemotherapy.

Introduction

The incidence and mortality of patients with cancer increases with age. Sixty per-

cent of all cancers and 70% of cancer mortality is found above 65 years of age [1]. As a result of the ageing population in western countries the demand for care of older people with cancer will strongly increase in the coming decades, also due to comorbidity, diminished organ functions, impairment of daily vital functions and development of cognitive dysfunctions. It seems to be logical to use biologic age as an indicator for health risks in the elderly but it is not a very sensitive and specific risk marker. The concept of frailty may be more valuable. Comprehensive geriatric assessment (CGA) provides information on the functional status of older cancer patients [2, 3, 4], consisting of objective information on comorbidity, functional status, nutritional status and psychosocial status. CGA can therefore disclose the existence of geriatric syndromes, which may complicate cancer treatment and vice versa may deteriorate during the course of treatment.

Several cross sectional studies have demonstrated associations between CGA and toxicity, morbidity and mortality during cancer treatment in older patients [5, 6, 7, 8, 9, 10, 11]. The effects of chemotherapy on cognitive function have been extensively studied prospectively in women with breast cancer [12, 13]. In other types of cancer, geriatric assessment has been studied more scarcely [14, 15]. Deterioration of cognition during chemotherapy has been hypothesized to be due to either direct chemical toxicity affecting neuroneogenesis, or by indirect effect through an increased (auto)inflammatory reaction [16, 17].

In the present study, we describe a basic GA of 202 cancer patients aged 70 years and above, with the aim to assess its prognostic value for treatment with chemotherapy, both with respect to the probability to complete chemotherapy and with respect to survival probabilities. Furthermore, among 51 patients the assessment was repeated after at least four courses of chemotherapy or at six months after start of treatment with the aim to assess the impact of chemotherapy on GA.

Patients and Methods

Patients

Between May 2004 and September 2007 all patients with cancer older than 70 years of age (n=202) for whom chemotherapy was prescribed by their medical oncologist in the hospital of the Reinier de Graaf Groep (Delft, the Netherlands), were prospectively assessed before chemotherapy using the following tests: Mini Nutritional Assessment (MNA), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Groningen Frailty Indicator (GFI) and Mini Mental State

Examination (MMSE). The tests were performed by trained nurses. All patients who underwent Geriatric Assessment (GA) started with chemotherapy. The test evaluation did not induce any delay in chemotherapy that the patients received. Patients completing at least four cycles of chemotherapy were again assessed by GFI and MMSE at the end of chemotherapy or six months after the start of chemotherapy. If indicated by the test results, a dietician and/or a geriatrician were consulted.

The MNA is a stepwise test and is comprised of two sections. First, there is the screening section (6 items). When the score is less than 12 points, indicating the possibility of malnutrition, the assessment section (12 items) is filled in. With the assessment section, a score of 24-30 points is indicative of being well-nourished, 17-23.5 points for being at risk of malnutrition, and a score less than 17 points for being malnourished. The test makes it possible to identify patients at risk for malnutrition, before severe changes in weight or albumin levels occur [18, 19]. This scoring system for malnutrition has a sensitivity of 96%, specificity of 98% and positive predictive value of 97% [20].

The IQCODE is a well validated instrument that screens for cognitive decline by interviewing family members or care givers [21]. The 16 items are rated on 5-point Likert scales, ranging from much improved to much worsened, and the average score is used in the analyses that ranges from 1 to 5. We used the short Dutch translation IQCODE-N [22]. In clinical settings, a cut-off score of 3.31 is a reasonably balance between sensitivity and specificity on the outcome of cognitive decline [23, 24]. Patients with a score of 3.30 or higher were examined by a geriatrician.

The risk for individual mortality, which can be seen as the ultimate outcome of age and frailty, can be predicted better by frailty than by chronologic age [25, 26]. The GFI has been developed as a simple screening instrument for frailty and a case finder for elderly patients who would benefit from integrated (geriatric) care [27, 28]. The GFI screens on physical, cognitive, social and emotional items. The maximum score is 15 points (see appendix). Patients scoring 4 or more points were considered moderately frail and were examined by a geriatrician.

The MMSE has been tested extensively and is considered to be a standard test for cognitive function. Sensitivity of the MMSE for cognitive dysfunction is 88%, the specificity is 93% [29, 30, 31, 32]. Patients scoring 24 points or less were seen by a geriatrician.

Statistical analysis

Categorical variables are presented as numbers and percentages and continuous variables as means ± standard deviations (SD), with their range. Chi-square tests were used for the analysis of categorical variables. Survival probabilities were estimated using Kaplan Meier curves and the log-rank test was used to test for difference in survival between categories of baseline CGA data. Cox proportional hazard regression was used to calculate hazard ratios (for MNA 2 categories were used: well nourished and risk of malnutrition / malnourished). Hazard ratios were adjusted for sex, age, purpose of chemotherapy (using 3 categories: adjuvant/curative; palliative and unknown) and type of malignancy (using 5 categories: digestive tract; breast cancer; ovarian cancer; hematological malignancies; other or missing). Changes in GA data over time were analyzed using the paired sample t-test. A p value less than 0.05 was considered significant. SPSS 17.0 for Windows® (SPSS inc. Chicago, IL.) was used for statistical analyses.

Results

Table 1 shows the baseline characteristics of the 202 included patients: 90 men (45%) and 112 women (55%). The mean age was 77.2 years (range 71—92). Fifty percent of patients received at least four cycles of chemotherapy. The duration of the follow-up, defined as the difference between the date of the first GA and the date of the last follow-up, showed a median of nine months (range 1-33).

Table 2 shows the results of geriatric assessment at baseline. With MNA, 65% of the patients were well nourished, while 30% of the patients were at risk for malnutrition and 3% were malnourished. A MMSE score of 24 points or lower, meaning a serious cognitive reduction, was seen in 10% of the patients. IQCODE showed an average score of 3.10 points. A GFI score of 4 or more points, meaning increased frailty, was found in 37% of the patients.

Table 3 depicts the results comparing less than 4 versus 4 or more chemotherapy cycles. With MNA and MMSE , there was a significant difference between the number of patients who underwent less than 4 cycles compared to patients who underwent 4 cycles or more. The mean reasons for not finishing the 4 cycles of chemotherapy were cancer progression, toxicity and insufficient benefit.

Figure 1 shows the Kaplan-Meier curves of overall survival according to predefined cut-off scores for the MNA, IQCODE, GFI and MMSE. Patients scoring lower than 24 points for MNA and 4 or more points for GFI showed significantly

worse survival ($p < 0.001$ and $p = 0.007$, respectively).

Table 4 gives the hazard ratios for mortality, indicating that a worse MNA score was associated with an increased mortality risk with a hazard ratio (HR) of 2.19 (95% confidence interval [CI]: 1.42-3.39; p<0.001) and a worse GFI score was associated with an increased risk with a HR of 1.80 (95% CI: 1.17-2.78; p=0.007). The sex- and age-adjusted hazard ratios for mortality were largely unaffected (model 1). When we additionally adjusted for the purpose of chemotherapy and type of malignancy, the hazard ratios for mortality with worse MNA and GFI scores were 2.54 (95% CI: 1.55-4.15; p<0.001) and 2.00 (95% CI: 1.26-3.17; p=0.004), respectively (model 2).

For the 51 patients with complete data for MMSE and GFI scores at baseline and after four or more cycles of chemotherapy, the MMSE showed a statistically significant deterioration after the chemotherapy (p=0.04; see Table 5).

Discussion

In this study, a basic GA was obtained of patients with cancer above the age of 70 years who were treated with chemotherapy. After at least four cycles of chemotherapy or at six months after the start of treatment, the GA was partly repeated with GFI and MMSE. The aim of this study was to develop tools for medical oncologists in their advice concerning treatment of elderly patients with chemotherapy. Malnutrition and cognition appeared independently related to the probability not to complete chemotherapy, while malnutrition and frailty (defined by GFI of 4 or more points) were associated with increased mortality. In addition, MMSE deteriorated slightly during the course of chemotherapy.

Traditionally, the Karnofsky Performance Scale or the World Health Organisation scores are used to determine the performance status of cancer patients. However, geriatricians have developed other scales to assess the functional status of older patients, for instance with ADL, IADL and the Charlson Comorbidity Index. We pragmatically selected the GFI, IQCODE, MMSE and MNA tests for performing a GA, striving for a maximum of 45 minutes to complete the interview. For the second assessment we repeated the GFI and MMSE. The IQCODE could not be used in the second assessment, because this instrument gives information on cognitive function over the past ten years. With the MMSE it is possible to measure deterioration after a short period. The used batch of tests should give a broad spectrum of data for coverage of GA with little overlap between the tests.

Approaches that are often used to assess functional status of older cancer patients are the Vulnerable Elders Survey (VES-13) [33], the abbreviated CGA (aCGA) [34], the clinical criteria by Fried et al. [35], the Edmonton Frailty scale [36] and the Groningen Frailty Indicator [37]. Puts et al. [38] demonstrated the importance of psychological markers in the concept of frailty. They showed that frailty was an independent risk factor for a decline in physical functioning, institutionalization and mortality. To measure frailty, the GFI is a short and easy practical instrument, and it seems a reasonable and manageable alternative compared to chronological age as a selection criterion for interventions [27]. Slaets et al. investigated the predictive values of chronologic age and frailty and the predictive power of the GFI in clinical studies comparing the GFI with the Quality of life Questionnaire (QLQ) C-30, the Charlson comorbidity index (CCMI) and the 10- to 30-day morbidity index. The GFI could predict most of the QLQ C-30 scales significantly. They found clinical relevant and significant differences between the frail and the nonfrail groups in mean scores on physical-, role-, and emotional function and fatigue [37]. The present analysis also showed a relation between GFI and survival, which remained significant after multivariable adjustment for sex, age, purpose of chemotherapy and type of malignancy.

The results of the MNA were almost identical with the findings of Toliusiene et al, who found that 50% of older men with prostate cancer were at risk for malnutrition [18]. Patients at risk were referred to a dietician because weight loss, low body mass index (BMI) and poor nutritional status are associated with increased risk of mortality, and more depressive symptoms [39, 40, 41, 42]. In the present study patients with normal MNA scores had a higher probability to complete pre-planned chemotherapy and a better survival, also after adjusting for the confounders mentioned earlier for GFI.

With MMSE, 11% of the patients showed serious cognitive impairment. Other studies found cognitive impairment in 25% to 38% of patients [3, 43, 44, 45, 46]. The present study showed, that a worse score for MMSE was associated with a larger probability of not completing 4 or more cycles of chemotherapy. Furthermore, the MMSE score at the second assessment in a limited number of patients was somewhat worsened compared to the assessment at baseline. Although this difference was significant, it did not appear to be a clinically meaningful difference. Comparison with other studies is difficult because there is no consistency in the definitions of cognitive dysfunction used in the literature [47, 48]. Hurria et al. found that fifty percent of the patients of 65 years or older, having received chemotherapy, reported cognitive decline 6 months after chemotherapy, especially concerning declined memory and the ability to learn new in-

formation [14]. The duration of cognitive impairment after chemotherapy is not clear. Some studies reported cognitive dysfunction in patients 2 to 10 years post chemotherapy [49, 50] but most patients in these studies were younger than 65 years. For patients over 70 years of age severity of cognitive impairment is probably more important than its duration. Fried et al. reported that if the outcome for a certain treatment was cure at the cost of severe functional- or cognitive impairment, 74.4 % and 88.8 % of serious ill patients, respectively, would not choose this treatment [44].

The multivariate analysis of the present study stipulates the importance of screening with MNA and GFI, as poor test results predicted for an increased mortality rate. The MMSE might contribute to the prediction whether chemotherapy can be completed, which was more powerful shown for the MNA. The IQCODE, which gives information of cognitive function over the past decade, did not show any predictive power in the present GA. Both MNA and GFI seem to be promising predictive screening tests for outcome when chemotherapy is considered in elderly patients with cancer.

A limitation of this study is the heterogeneity of patients with a wide diversity of types of cancer, different stages of cancer and different treatments. Furthermore, it could be that there are unaccounted confounders for example alcohol consumption, smoking and socio-economic status. Comparison with other studies is difficult because of the paucity of data in the literature. Further research is needed for clarification of the tools available for geriatric assessment. In this way, the care for older patients with cancer, treated with chemotherapy can result in a more tailor-made approach, aiming for optimal balance between efficacy and toxicity of treatment.

Table 1
Characteristics of patients (n = 202)

		years	SD	
Age	Mean	77	4.22	
	Minimum	71		
	Maximum	92		
			n	**%**
Gender	Male		90	45
	Female		112	55
Number of chemotherapy cycles	< 4		74	37
	≥ 4		118	58
	unknown		10	5
Type of malignancy	Upper digestive tract		19	9
	Colorectal cancer		60	30
	Breast cancer		34	17
	Ovarian cancer		20	10
	Hematological malignancies		36	18
	Other types*		28	14
	Unknown		5	2
Purpose of chemotherapy	Adjuvant/curative		80	40
	Palliative		111	55
	Unknown		7	3
	Missing		4	2

*The category other types of malignancy consisted mainly of prostate cancer (n=12), lung cancer (n=7) and urothelial cell cancer (n=5)

Table 2
Results of the geriatric assessments at baseline (n=202)

Test	Score	n	%
MNA	well nourished (>12 pts* and 24-30 pts[§])	131	65
	risk of malnutrition (17-23.5 pts[§])	60	30
	malnourished assessment (less than 17 pts[§])	5	3
	unknown	6	2
MMSE	> 24 pts	178	88
	≤ 24 pts	21	10
	unknown	3	2
IQCODE	> 3.30 pts	30	15
	≤ 3.30 pts	163	81
	Unknown	9	4
GFI	<4 pts	127	63
	≥4 pts	75	37

*MNA screening section
[§] MNA assessment section

Table 3.
Baseline test results in 192 subjects, comparing patients who received less than four cycles to patients who received four or more cycles of chemotherapy

		Number of cycles				
		<4 (n=74)		**≥4** (n=118)		
Test	**Score**	**n**	**%**	**n**	**%**	***p*- value**
MNA:	well nourished	37	51	86	75	0.001
	risk of malnutrition/ malnourished	35	49	29	25	
	missings	2		3		
IQCODE:	≥ 3.3	14	20	15	13	0.20
	< 3.3	55	80	99	87	
	missings	5		4		
GFI:	< 4	42	57	79	67	0.15
	≥ 4	32	43	39	33	
MMSE:	> 24	64	89	113	97	0.04
	≤ 24	8	11	4	3	
	missings	2		1		

For 10 patients it was unknown whether they finished 4 cycles because they just started and were ongoing with chemotherapy.
Well nourished meaning >12 pts in MNA screening section or 24-30 pts in the MNA assessment section; risk of malnutrition /malnourished meaning less than 24 pts in the MNA assessment section.
P-values are obtained from Pearson chi-square tests (missings were not included in chi-square tests).

Table 4.
Hazard ratios (95% confidence intervals) for mortality in 202 cancer patients

Test	Score	Crude	Model 1	Model 2
MNA:	well nourished	1.00	1.00	1.00
	risk of malnutrition / malnourished	2.19 (1.42-3.39)	2.34 (1.49-3.66)	2.54 (1.55-4.15)
		p<0.001	*p*<0.001	*p*<0.001
IQCODE:	≥ 3.3	1.00	1.00	1.00
	< 3.3	0.84 (0.46-1.53)	0.86 (0.47-1.57)	0.93 (0.49-1.73)
		p=0.57	*p*=0.63	*p*=0.81
GFI:	< 4	1.00	1.00	1.00
	≥ 4	1.80 (1.17-2.78)	1.89 (1.22-2.94)	2.00 (1.26-3.17)
		p=0.007	*p*=0.005	*p*=0.004
MMSE:	> 24	1.00	1.00	1.00
	≤ 24	1.05 (0.51-2.18)	0.99 (0.48-2.07)	0.92 (0.44-1.93)
		p=0.89	*p*=0.87	*p*=0.82

Baseline MNA, IQCODE, GFI and MMSE data are dichotomized.
Well nourished meaning >12 pts in MNA screening section or 24-30 pts in the MNA assessment section; risk of malnutrition / malnourished meaning less than 24 pts in the MNA assessment section.
Model 1: adjusted for sex and age;
Model 2: additionally adjusted for purpose of chemotherapy and type of malignancy.

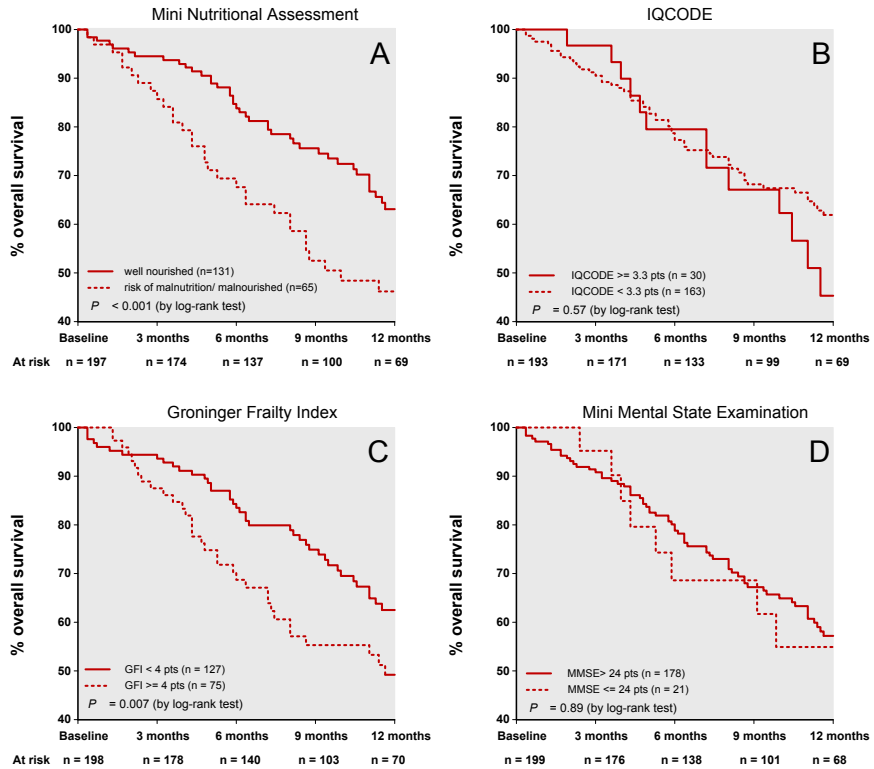
Table 5
Differences between baseline- and second assessment (after at least 4 cycli) of MMSE and GFI (n=51)

	At baseline			2e assessment					
	Median	P25	P75	Median	P25	P75	Mean change	SE	*p*-value*
MMSE	30	28	30	29	27	30	-0.86	0.41	0.041
GFI	2	1	3	2	1	5	0.24	0.33	0.476

*t-test for paired samples

Figure 1

Kaplan-Meier curves of overall survival for different categories of MNA **[A]**, IQCODE **[B]**, GFI **[C]** and MMSE **[D]**.



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