Predicting outcome in older patients with cancer: Comprehensive geriatric assessment and clinical judgment

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Abstract

Objectives: Comprehensive Geriatric Assessment (CGA) has been incorporated into geriatric oncology to prevent unfavorable outcome from anticancer treatment. This study determined the value of CGA and medical oncologist’s clinical judgment in predicting unfavorable outcome and explored whether treatment decisions can be based on CGA.

Patients and Methods: In this prospective cohort study, a multidomain CGA was performed by a geriatric nurse and geriatrician in 110 consecutive patients aged ≥70 years, newly referred to a multidisciplinary oncology clinic. CGA domains included comorbidity, polypharmacy, mood, cognition, nutrition, functionality and physical performance. Medical oncologist’s clinical judgment on expected tolerance of standard treatment was noted (N = 62). Unfavorable outcome was defined as any grade three chemotherapy toxicity, dose reduction, postponement of treatment, death before start of treatment and early progression before first evaluation of treatment (N = 80).

Results: CGA identified multidomain problems in 77 out of 110 patients (70.0%) and the medical oncologist had doubts about standard treatment tolerance in 30 out of 62 patients (48.4%). Unfavorable outcome occurred in 48 out of 80 patients (60%) who received anticancer treatment but could not be predicted by CGA, medical oncologists’ clinical judgment or their combination. There was discrepancy between CGA and clinical judgment in 24 out of 62 patients (38.7%).

Conclusion: Neither CGA, medical oncologist’s clinical judgment or a combination could predict unfavorable outcome in our heterogeneous sample. CGA and clinical judgment did not align in more than one-third of patients.

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1. Introduction

For medical oncologists, predicting treatment toxicity and clinical outcome in older patients with cancer is challenging while complication rates are high [1–3]. Treatment decisions are mostly based on clinical judgment and subjective performance scales such as the Karnofsky performance score. However, these scales are not as sensitive in older populations as in younger populations [4,5], potentially leading to suboptimal treatment of older patients with cancer [6,7]. Moreover, objective reasoning is desired to assist medical oncologists in their advice to adapt or refrain from standard treatment. One of the main goals of a Comprehensive Geriatric Assessment (CGA) is to objectively identify patients who will benefit from anticancer treatment to prevent under- and overtreatment of older patients with cancer [8–11] and to initiate interventions and supportive care based on impaired domains.

CGA in older patients with cancer is valuable to detect impairments and supportive care based on impaired comorbidity, nutrition, and functionality have been associated with worse outcome i.e. more toxicity or worse survival in older patients with cancer [15,17,18]. Furthermore, physical performance is highly predictive of future health outcomes in non-oncological populations.

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Patients received written information about their appointments and a questionnaire on demographic data, social status, mobility, history of falls, functionality, and cognitive complaints was conducted. Functional dependence was assessed using the Katz Index for Activities of Daily Living (ADL) with ≥ two points indicating dependency in ADL [22] and Lawton-Brody scale for Instrumental ADL (IADL) with > seven points indicating dependency in IADL [23].

2.2. Self-Assessment

A geriatric nurse conducted a CGA consisting of: depressive symptoms, cognition, nutritional status, and physical performance. Depressive symptoms were measured using the Geriatric Depression Scale (GDS), > four points indicating depressive symptoms [24,25]. Cognition was assessed using the Mini Mental State Examination (MMSE), <24 points indicating cognitive impairment [26]. The Mini Nutritional Assessment-Short Form (MNA-SF) assessed the nutritional status, ≤ eleven points indicating risk of malnourishment [27]. Additionally, weight and height were measured to calculate body mass index (BMI).

Physical performance was tested using the Short Physical Performance Battery (SPPB), Timed-Up and Go (TUG) test and handgrip strength (HGS). The SPPB included balance tests in which three positions (side-by-side, semi-tandem and tandem) had to be maintained for ten seconds, four-meter walk test (cutoff <4.82 s) and chair stand test (CST) (cutoff ≤11.19 s) [28]. For the four-meter walk test, patients walked four meters at their usual pace and the fastest time of two measurements was scored [28]. The CST measured the fastest time needed to stand up five times and sit down again while keeping the arms crossed over the chest [28]. These tests formed a SPPB composite score of zero to twelve points, < ten points indicating mobility limitations [28]. For the TUG, patients were asked to stand up from a sitting position without using their hands, walk three meters, walk around a cone, walk three meters back and return to sitting position without using hands, as fast as possible, > fourteen seconds considered low performance [29,30]. HGS was measured using a hydraulic hand dynamometer (Jamar Handheld Dynamometer) in standing position, the shoulder adducted and elbow flexed at 90 degrees, forearm and wrist in neutral position. Patients were instructed to squeeze as hard as possible with alternating hands for three times [31]. Maximal HGS was analyzed continuously in kilograms and dichotomized into low HGS <30 kg for men and <20 kg for women and normal HGS [32]. Patients who were unable to perform or finish a test were given a score of 0 kg HGS or 100 s for four-meter walk test, CST (or used hands to stand up) and TUG to include these patients in analyses [33].

2.4. Physicians Assessment

A geriatrician evaluated comorbidity using the Charlson Comorbidity Index (CCI) and polypharmacy, which was defined as use of ≥ five medications. The CCI questions the presence of nineteen comorbidities scored based on their severity (0–39 points), ≥ two points indicating multimorbidity [34]. Tumor characteristics including cancer type and stage were documented.

2.5. Decision Making

The medical oncologist’s clinical judgment was dichotomized into no doubts versus doubts. CGA results were subdivided into seven domains including comorbidity (CCI), polypharmacy, mood (GDS), cognition (MMSE), nutrition (MNA-SF), functionality (history of falls, ADL and IADL), and physical performance (SPPB, TUG, and HGS) [12]. Aforementioned cut-off points were used to determine whether problems on each of the domains were identified. CGA result was dichotomized into no/one domain problem versus multidomain problems identified.

2.6. Follow-up and Outcome Measures

Patients’ charts were followed. Information regarding given treatment, treatment toxicity, disease progression and survival was documented. Unfavorable outcome was chosen as outcome measure because it is of importance to not only predict treatment toxicity, but other outcomes that should be avoided as well i.e. early progression of disease and death before start of treatment. Systemic treatment in the metastatic setting is aimed at prolonged survival with preservation of
quality of life (QoL). It is important to know the patients’ individual goals of life in light of the estimated prognosis. An incorrect expectation of prognosis limits making informed choices about the potential harms of treatment and the potential benefits of palliative care and thus affects QoL. [35] In this study unfavorable outcome is defined as any grade three or higher chemotherapy toxicity (according to CTCAE 4.0) before every new cycle of treatment, dose reduction, postponement of treatment more than one week, death before start of planned treatment, and early clinical progression (based on either imaging, tumor markers or clinical deterioration) or mortality before first evaluation (eight to twelve weeks) of treatment. Upfront dose reduction was not considered unfavorable outcome. Due to the heterogeneity of treatments, unfavorable outcome was separately analyzed in patients treated with chemotherapy.

2.7. Statistical Analysis

Analyses were performed using SPSS version 25.0 (IBM Corporation, Armonk, USA). Descriptive statistics were used to describe basic features of the data, continuous data presented as mean ± standard deviation (sd) if normally distributed and median [interquartile range (IQR)] if distribution was skewed. Individual elements of CGA were tested as determinants of the medical oncologist’s clinical judgment using multiple logistic regression analysis. The associations between CGA result, medical oncologist’s clinical judgment and a combination of CGA and clinical judgment with unfavorable outcome were analyzed using logistic regression analysis. These analyses were performed separately for individual domains of CGA. Diagnostic accuracy of CGA result, medical oncologist’s clinical judgment, and their combination to predict unfavorable outcome was determined by calculating sensitivity, specificity and area under the curve (AUC). AUC was defined as low <0.70, acceptable 0.70–0.80 and excellent >0.80. The relation between CGA result and medical oncologist’s clinical judgment was analyzed using cross tabs and chi-square test. P-values of ≤0.05 were considered statistically significant.

3. Results

3.1. Patient Characteristics

The study population of older patients with cancer had a mean age of 77.9 ± 5.2 years old and 54.5% was male. Gastro-intestinal cancers were most represented and the majority of patients suffered from metastatic cancer (54.1%). Most patients were treated with chemotherapy alone (N = 48; 43.6%). Table 1 shows cancer-related patient characteristics.

3.2. CGA

Table 2 shows patient characteristics obtained by CGA. Multimorbidity was present in 43.6% and polypharmacy in 52.8% of patients. An indication of depressive symptoms was present in 18.4% of patients, of cognitive impairment in 6.9% and risk of malnourishment in 52.4%. There were problems identified in the domain of functionality including ADL-, IADL dependency and history of falls, in 37.9% of patients and physical performance problems were present in 61.3%. CGA did not reveal any problems in eleven patients (10.0%). In 22 patients, CGA revealed a single domain problem (20.0%), which was predominantly the domain of physical performance, while none of these patients had problems within the domain of mood or cognition. In the 77 patients with multidomain problems (70.0%), the domain of physical performance was also the most affected, followed by the domain of polypharmacy, nutrition, and comorbidity.

3.3. Clinical Judgment

Medical oncologist’s clinical judgment was recorded in 62 patients. The medical oncologist had doubts about administering standard anticancer treatment in 30 patients (48.4%). Of these 30 patients, standard anticancer treatment was started in seven patients and non-standard anticancer treatment in the form of reduced dosage or less toxic treatment was started in four patients. In five patients treatment was planned but because of clinical deterioration not received and in three patients doubts led to refraining from treatment. Given treatment was unknown in eleven patients due to loss to follow-up or treatment elsewhere. Chance of doubts by the medical oncologist was higher if patients used a walking aid, in case of polypharmacy, a high GDS score, a low MNA-SF score, a history of falling, low ADL and IADL score, inability to perform the tandem balance test, low total SPPB score and prolonged TUG (Supplementary Table 1, subdivided into elements that are part of a standard oncological consult and elements specifically added by CGA). Polypharmacy and the use of a walking aid were independent predictors of doubts by the medical oncologist.

3.4. Unfavorable Outcome

An overview of the number of patients with available data is shown in Fig. 1. Of the 110 patients, unfavorable outcome could not be determined in 30 patients because they did not receive any anticancer treatment (patient’s preference (N = 8), were advised to refrain from therapy by the medical oncologist or multidisciplinary
In 26 of these 30 patients, CGA identified multidomain problems (86.7%). The medical oncologist had doubts about initiating standard treatment in fourteen out of seventeen of these patients (82.4%). CGA result and medical oncologist’s clinical judgment overlapped in fifteen out of seventeen patients (88.2%). In conclusion, analyses with unfavorable outcome were performed in 80 patients. Analyses with chemotherapy-related unfavorable outcome were performed in 60 patients, since 20 patients received another type of anticancer treatment such as hormonal therapy. These 60 patients included 47 patients who received chemotherapy (N = 1 missing due to treatment elsewhere), four patients who received chemoradiation (N = 1 missing due to treatment elsewhere) and nine patients who were planned to receive chemotherapy but eventually did not due to early progression or death prior to the start of chemotherapy treatment. The medical oncologist’s clinical judgment was known in 62 patients, of whom 45 also had data on unfavorable outcome and 35 patients on chemotherapy-related unfavorable outcome.

In total, 48 out of 80 patients (60.0%) and 45 out of 60 patients (75.0%) who received chemotherapy, experienced an unfavorable outcome. The prevalence of uncomplicated treatment and unfavorable outcome stratified by CGA result and medical oncologist’s clinical judgment is shown in Fig. 2. Of the 80 patients of whom both CGA result and outcome was known, CGA showed a one domain problem in 29 patients (36.3%). Treatment in twelve of these patients (41.4%) was indeed uncomplicated. If problems in ≥ two domains were identified by CGA, treatment was uncomplicated in 20 out of 51 patients (39.2%). Of the 45 patients of whom both medical oncologist’s clinical judgment and outcome were known, the medical oncologist had no doubts about prescribing standard treatment in 29 patients (64.4%). Treatment in thirteen patients (44.8%) was indeed uncomplicated; remaining patients experienced complications such as early progression and chemotherapy toxicity including neuropathy and neutropenia. If the medical oncologist did have doubts, treatment was uncomplicated in five out of sixteen patients (31.2%). No significant associations between CGA result, individual domains of CGA, medical oncologist’s clinical judgment nor a combination of CGA and clinical judgment with unfavorable outcome were found. The nutritional domain was borderline significant in the chemotherapy subgroup (p = 0.050) (Table 3).

![Fig. 1. Flowchart of inclusion of patients in the MOOP cohort. MOOP: Multidisciplinary Oncology Older Patients; CGA: Comprehensive Geriatric Assessment.](image-url)
Sensitivity of CGA result to predict unfavorable outcome was 64.6%, specificity 37.5% and AUC 0.51. For the medical oncologist’s clinical judgment, sensitivity was 40.7%, specificity 72.2% and AUC 0.57, and for their combination sensitivity was 29.6%, specificity 72.2% and AUC 0.51. Similar results were found if diagnostic accuracy was calculated in the chemotherapy subgroup, except specificity was slightly higher for CGA result (53.3%). Conclusions remained similar if the association between CGA result and unfavorable outcome was only assessed in the 45 patients of whom the medical oncologist’s clinical judgment was known.

Fig. 2. Outcome stratified for Comprehensive Geriatric Assessment result and medical oncologists’ clinical judgment. Diagram showing uncomplicated treatment and unfavorable outcome according to Comprehensive Geriatric Assessment result (2a) and medical oncologist’s clinical judgment (2b). CGA: Comprehensive Geriatric Assessment.

Table 3
Association between comprehensive geriatric assessment result/medical oncologists’ clinical judgment and unfavorable outcome.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Unfavorable outcome</th>
<th>Unfavorable outcome, chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>OR</td>
</tr>
<tr>
<td>CGA result, multi-domain problems</td>
<td>80</td>
<td>1.094</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>80</td>
<td>0.680</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>78</td>
<td>0.582</td>
</tr>
<tr>
<td>Mood/depression</td>
<td>64</td>
<td>0.955</td>
</tr>
<tr>
<td>Cognition</td>
<td>75</td>
<td>0.419</td>
</tr>
<tr>
<td>Nutrition</td>
<td>76</td>
<td>1.810</td>
</tr>
<tr>
<td>Functional</td>
<td>74</td>
<td>1.734</td>
</tr>
<tr>
<td>Physical performance</td>
<td>78</td>
<td>1.112</td>
</tr>
<tr>
<td>Medical oncologists’ clinical judgment, doubts</td>
<td>45</td>
<td>1.787</td>
</tr>
<tr>
<td>Combination CGA and clinical judgment, multi-domain problems and doubts</td>
<td>45</td>
<td>1.095</td>
</tr>
</tbody>
</table>

N: number; OR: odds ratio; CI: confidence interval; CGA: Comprehensive Geriatric Assessment; NA: not applicable. For the cognitive domain analysis could not be performed for chemotherapy-related unfavorable outcome, due to low number of patients that showed problems within the cognitive domain. Analyses were performed with N = 80 for unfavorable outcome and N = 60 for chemotherapy-related unfavorable outcome. P-value of < .05 was considered statistically significant and given in bold.
3.5. CGA Versus Medical Oncologist

For 62 patients, both CGA result and medical oncologist’s clinical judgment were available. There was discrepancy between CGA result and medical oncologist’s clinical judgment in 24 patients (38.7%) (Fig. 3). In the majority of these patients, CGA identified multidomain problems, while the medical oncologist did not identify these problems or did not consider them a problem for prescribing standard anticancer treatment. Most frequently disturbed domains in these patients were nutrition and physical performance. Multidomain problems identified by CGA and doubts of the medical oncologist were associated with one another (p = 0.022).

4. Discussion

This prospective cohort study showed that in more than two-thirds of older patients with cancer referred to the medical oncologist, CGA identified multidomain problems, which mainly concerned physical performance. In almost half of referred patients the medical oncologist had doubts about initiating standard anticancer treatment. Unfavorable outcome defined as chemotherapy toxicity, dose reduction, postponement of treatment, death before start of treatment and early progression before first evaluation of treatment was highly prevalent (60%), but could not be predicted by CGA, medical oncologist’s clinical judgment, nor by their combination. Unfavorable outcome still occurred in more than half of patients who were considered fit for treatment by either CGA or medical oncologist. On the other hand, treatment was uncomplicated in at least one-third of patients who were considered unfit by either CGA or medical oncologist. CGA and medical oncologists came to different conclusions in more than one-third of patients, CGA being more reserved than the medical oncologist, mainly due to problems identified within the domain of nutrition and physical performance.

The findings of this study endorse the prevalence of geriatric impairments in older patients with cancer [12,20]. Furthermore, they indicate the importance of improving patient selection for anticancer treatment, adequate treatment adjustments, and optimizing supportive care during anticancer treatment, since 60% of all patients and 75% of patients who received chemotherapy experienced some form of unfavorable outcome such as early progression and chemotherapy toxicity. The prevalence of unfavorable outcome was even higher than other studies have reported [1–3], which can be attributed to the definition of unfavorable outcome which included not only treatment toxicity but also early progression and death before start of treatment. This shows the importance of not only aiming at predicting treatment toxicity. Especially the prevalence of patients who were unable to receive any treatment was relatively high (nine of 80 patients), which could be due to the academic hospital population which included tumor types with generally worse prognoses.

Although several studies showed that CGA was a better predictor of treatment toxicity than clinical judgment [36,37], neither CGA nor medical oncologist’s clinical judgment was associated with unfavorable outcome in this study. The relatively high specificity of the medical oncologist’s clinical judgment might indicate that doubts about tolerating standard anticancer treatment should lead to caution and maybe even refraining from anticancer treatment. It should be noted that despite the medical oncologists hesitation towards treatment, treatment was still started or intended in several patients. Reasons could be that medical oncologists are inclined to give patients the benefit of the doubt if patients are motivated to undergo treatment [38]. This emphasizes the need for objective measures in addition to clinical judgment to support medical oncologists to refrain from treatment. Moreover, it highlights the importance of acknowledging the medical oncologist’s doubts, educating medical oncologists on treatment goals in geriatric oncology and on discussing best supportive care as an alternative for palliative treatment with expected low benefit [39,40] [41].

CGA however, was slightly more reserved with relatively higher sensitivity. No or single domain problems seemed to be a better indicator of uncomplicated treatment than multidomain problems for unfavorable outcome. Therewith, multidomain problems detected by CGA should not implicitly lead to modified treatment plans. This could lead to undertreatment, as supported by more than one-third of patients with multidomain problems who still underwent treatment without complications. Though this could have been influenced by interventions that were initiated before and during treatment such as advice from a dietician, physiotherapist and medication alterations, it might indicate the need for further evaluation and consideration with the patients and their families to optimize treatment strategies.

When interpreting the results of this study it is important to consider the following points. First, the relatively small study population was heterogeneous in type, stage and, treatment of cancer as well as comorbidities. The toxicity of treatment varies between different chemotherapy regimens, and the prognosis varies greatly between different cancer types. For these reasons, it is difficult to draw firm conclusions from the study for specific groups of patients. Secondly, interventions were initiated immediately if CGA identified problems. This could have led to extra support from a dietician or physiotherapist for example, which may have had a positive influence on treatment outcome in this group. This study does not provide data on QoL or the development of functional status. It is known that not all unfavorable outcome leads to poorer QoL, for instance grade 3 leukopenia. Further research should be directed towards improving objective patient selection for anticancer treatment and identifying patients who are prone for unfavorable outcome, as well as optimizing treatment adjustments and supportive care during anticancer treatment to improve outcome. During the decision-making process, dedicated attention should be given to assess the patients’ goals and preferences in anticancer treatment. Shared decision-making should be pursued and the patients’ thoughts on how to maintain and improve quality of life should be guiding. Also, it is of importance to increase diagnostic accuracy of CGA to predict the risk of unfavorable outcome.

5. Conclusion

In conclusion, unfavorable outcome was highly prevalent in a heterogeneous cohort of older patients with cancer treated with different

![Fig. 3. Discrepancy between Comprehensive Geriatric Assessment result and medical oncologists’ clinical judgment (N = 62). Discrepancy between Comprehensive Geriatric Assessment result and medical oncologist’s clinical judgment is indicated in grey shading. CGA: Comprehensive Geriatric Assessment.](image-url)
modalities, and could not be predicted by CGA, medical oncologist’s clinical judgment or by their combination. Unfavorable outcome was still highly prevalent in patients considered fit for treatment, while there was also a large number of patients with uncomplicated treatment who were considered unfit. Moreover, discrepancy between CGA and medical oncologist’s clinical judgment was high, both identifying different patients as fit or unfit for anticancer treatment. The results emphasize the need for more objective measures to identify older patients with a high risk of unfavorable outcome to provide reasoning for refraining from or adapting treatment. The main goal of CGA should remain identifying existing geriatric impairments to improve overall condition.

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Declaration of Competing Interest
Kathelijn S. Versteeg, Stéphanie M.L.M. Looijgaard, Monique S. Slee-Valentijn, Henk M.W. Verheul, Andrea B. Maier and Inge R.H.M. Konings declare that they have no conflict of interest.

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