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The impact of comprehensive geriatric assessment interventions on tolerance to chemotherapy in older people

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Background: Although comorbidities are identified in routine oncology practice, intervention plans for the coexisting needs of older people receiving chemotherapy are rarely made. This study evaluates the impact of geriatrician-delivered comprehensive geriatric assessment (CGA) interventions on chemotherapy toxicity and tolerance for older people with cancer.

Methods: Comparative study of two cohorts of older patients (aged 70+ years) undergoing chemotherapy in a London Hospital. The observational control group ($N=70$, October 2010–July 2012) received standard oncology care. The intervention group ($N=65$, September 2011–February 2013) underwent risk stratification using a patient-completed screening questionnaire and high-risk patients received CGA. Impact of CGA interventions on chemotherapy tolerance outcomes and grade 3+ toxicity rate were evaluated. Outcomes were adjusted for age, comorbidity, metastatic disease and initial dose reductions.

Results: Intervention participants undergoing CGA received mean of 6.2 ± 2.6 (range 0–15) CGA intervention plans each. They were more likely to complete cancer treatment as planned (odds ratio (OR) 4.14 (95% CI: 1.50–11.42), $P=0.006$) and fewer required treatment modifications (OR 0.34 (95% CI: 0.16–0.73), $P=0.006$). Overall grade 3+ toxicity rate was 43.8% in the intervention group and 52.9% in the control ($P=0.292$).

Conclusions: Geriatrician-led CGA interventions were associated with improved chemotherapy tolerance. Standard oncology care should shift towards modifying coexisting conditions to optimise chemotherapy outcomes for older people.

The number of clinically complex older people presenting to cancer services is increasing. There are often concerns that older, more comorbid or frail people may struggle to tolerate chemotherapy. This may result in chemotherapy not being offered or in planned treatment being modified or stopped early with potential negative implications for prognosis (Foote, 1998).

Strategies are sometimes used to reduce toxicity risk, for example, adapted treatment regimens (Schaich *et al*, 2002; Zinzani *et al*, 2002; Basso *et al*, 2008; Kotsori *et al*, 2010) or using granulocyte colony-stimulating factor (Repetto *et al*, 2003; Brugger *et al*, 2009). These strategies focus on adapting treatment and rarely include optimising patient factors (e.g. comorbidity, function) that may influence chemotherapy toxicity and/or tolerance (Wedding *et al*, 2007). Although oncology assessments include identifying patient factors to inform cancer treatment decisions (Blanco *et al*, 2008; Ring, 2008; Department of Health, 2012a),

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this assessment is rarely used to identify coexisting needs that may be modified by clinical interventions (Extermann and Hurria, 2007; Maas *et al*, 2007).

Comprehensive geriatric assessment (CGA) is the central technology of specialist geriatric medical practice. It involves a review of frailty, comorbidities, geriatric syndromes (e.g. falls, incontinence), mental health, functional difficulties and social circumstances. Although the term CGA may imply activity limited to assessment, it is in fact a larger clinical process with four parts: (1) screening, (2) assessment (including standardised tools to augment clinical history and examination), (3) goal-directed intervention and (4) follow through (Rubenstein *et al*, 1991). All parts of this process are integral to delivering evidence-based CGA.

Comprehensive geriatric assessment has a robust evidence base of effectiveness in several clinical settings: improved function and reduced institutionalisation in community-dwelling individuals (Stuck *et al*, 1993); similar benefits plus reduced mortality in older medical in-patients (Stuck *et al*, 1993; Ellis *et al*, 2011a, b), and reduced postoperative complications, shorter length of hospital stay and reduced mortality in orthopaedics and other surgery (Elliot *et al*, 1996; Harari *et al*, 2007; Gonzalez Montalvo *et al*, 2011).

Studies of CGA in the cancer literature have generally reported evaluations limited to the screening and/or assessment part of the CGA process, with assessment being largely tool-based (e.g. nutritional screening tool, cognitive score) without a comprehensive clinical review. Cancer studies including key elements of CGA, namely clinical review, intervention and follow through, are lacking (Wildiers *et al*, 2014). The differences between the evidence-based CGA clinical process and these more limited studies in the cancer literature were acknowledged in the recently published International Society of Geriatric Oncology (SIOG) consensus (Wildiers *et al*, 2014). International Society of Geriatric Oncology renamed the term CGA as 'GA' to reflect this disparity. Findings from studies investigating GA are difficult to compare with those of CGA given the lack of clinical intervention with GA.

Studies of GA in oncology have evaluated feasibility as a screening tool (Hurria *et al*, 2007) and influence on cancer treatment decision-making (Girre *et al*, 2008; Marenco *et al*, 2008). Some report its utility in predicting chemotherapy toxicity (Extermann *et al*, 2011; Hurria *et al*, 2011). The few studies investigating CGA show influence on improved survival following cancer surgery (McCorkle *et al*, 2000), influence on oncological decision-making, and that multiple CGA interventions are required in cancer populations (Caillet *et al*, 2011; Chaibi *et al*, 2011). To the authors knowledge however, there are no studies evaluating whether CGA, the clinical process (screening, assessment, intervention, follow through), influences tolerance to chemotherapy. The International Society of Geriatric Oncology recently highlighted the need for such studies (Wildiers *et al*, 2014), reiterated by UK national health policies now advocating comprehensive assessments for older people (based on the strong evidence for CGA in other settings) at the time of cancer treatment decision-making (Department of Health, 2010, 2012b).

The purpose of this study was to evaluate the impact of geriatrician-delivered CGA on chemotherapy toxicity and tolerance. A secondary aim was to evaluate the number of interventions required and made as a result of CGA in older people undergoing chemotherapy.

MATERIALS AND METHODS

Study design. A prospective cohort comparison study, comparing geriatrician-delivered CGA with usual oncology care.

Setting. The study was conducted in a London hospital providing cancer care to patients living locally and across South-East England. As with most UK hospitals, geriatricians and oncologists work within their own disciplines in the same hospital, but with no formal liaison between the two services. The service model to deliver geriatrician-led CGA was developed for the purposes of this study with stakeholder support from oncologists, nursing, therapies, voluntary organisations and executive management. It was based on existing CGA evidence and additionally moulded from insights derived during the early stages of the observational cohort study.

Participants. Participants included in this analysis were older patients (aged 70+ years) with cancer recruited at the start of chemotherapy (with or without radiotherapy). Potential participants were identified from oncology clinics and chemotherapy day units using the hospital electronic record system.

Exclusion criteria

- Age <70 years.
- Cancer treatment plan excluded chemotherapy.
- Chemotherapy had already started before they could be approached for participation.
- Lack of mental capacity to consent.
- Expected prognosis ⩽3 months.

Control and intervention study recruitment periods crossed, minimising potential period effect bias (control group October 2010–July 2012, intervention group September 2011–February 2013). This report is restricted to participants aged 70+ years recruited at the start of chemotherapy within two larger studies (one observational, one interventional) recruiting older people presenting to cancer services. The overall observational study was designed to identify comorbidities and CGA characteristics (using a CGA questionnaire) associated with poorer treatment tolerance in participants aged 65+ years receiving usual care. The overall intervention study aimed to investigate the impact of CGA interventions on cancer outcomes (including treatment tolerance and survival) in participants aged 70+ years. Both these studies included participants receiving a number of different treatment modalities including but not restricted to chemotherapy (i.e. also included surgical patients, radiotherapy, hormonal treatment, and so on). We report the outcomes of those recruited at the start of chemotherapy treatment, comparing the CGA intervention to usual care. Patients excluded from the presented analysis either received a non-chemotherapy treatment modality, were not recruited at the start of chemotherapy or were not aged 70+ years in the control group (to age match to the intervention group). Local and national ethics approval was obtained for the observational (09/H0178/65) and intervention study (11/LO/0695). All participants gave written informed consent for participation.

Interventions. All participants (control and intervention) completed a baseline self-reported screening questionnaire (called 'CGA-GOLD') containing evidence-based CGA questions (Chen *et al*, 2003; Terret *et al*, 2004; Hurria *et al*, 2005, 2007; Mohile *et al*, 2007) and a validated quality of life tool (QOL) (EORTC-QLQ-C30) (Aaronson *et al*, 1993) (questionnaire available in online Supplementary Material). The 70 control group participants received routine care only. Their CGA-GOLD responses were not shared with the oncology team. For the 65 intervention cohort participants, the CGA-GOLD questionnaire was used to stratify them into low or high risk. Low risk was defined as no self-reported active comorbidities, CGA issues or recent hospital admissions and 'no' or 'little' difficulties reported for all function and QOL questions. High risk was defined as 1+ reported active comorbidity and/or CGA issues and/or significant QOL/functional

difficulties (self-reported as 'quite a bit' or 'very much' difficulty). Additionally, telephone calls were made to clarify the need for high-risk patients with $\leqslant 2$ identified issues where the clinician anticipated it may be possible to manage these without full CGA. The telephone call either confirmed risk and need for CGA or identified that these few issues were already managed or could be managed remotely (e.g. dietitian referral for weight loss). Higher risk patients received CGA before commencing chemotherapy. The oncologist could additionally directly refer patients for CGA if they deemed it was clinically indicated. Figure 1 summarises the risk assessment pathway used for identifying those requiring CGA.

Comprehensive geriatric assessment covered domains as highlighted in the SIOG consensus (Wildiers *et al*, 2014). This included a full medical assessment, comorbidity management (e.g. diabetes, cardiac), management of geriatric syndromes (e.g. falls, incontinence) and review of functional and psychosocial difficulties. Cancer diagnosis, planned chemotherapy type and anticipated toxicities were taken into consideration when decisions were made regarding the need or type of intervention for a particular comorbidity or CGA issue. For example, tighter diabetic control, monitoring and pre-emptive plans for those to receive steroids with chemotherapy *vs* looser control if poor oral intake anticipated or not relevant in light of overall prognosis. Intervention plans were made for CGA/comorbidities identified as modifiable. Issues identified but not requiring interventions (either already being addressed or already optimised or not modifiable) were not included as interventions. The assessment and intervention plans were communicated to the oncologist (electronically) before starting chemotherapy, General Practitioner and patient. Further geriatrician support and follow through was available as needed. There were no other changes to oncology services during the study period.

Measures. Patient demographics, comorbidities, cancer-related data and outcomes were collected using hospital electronic patient records. Twenty-three CGA variables were collected predominantly through the CGA-GOLD questionnaire (comorbidity and CGA variable definitions available in online Supplementary Material).

The impact of CGA on chemotherapy tolerance and toxicity was evaluated by comparing the intervention and control cohorts as follows:

Coprimary outcomes:

- Grade 3–5 toxicity rate (National Cancer Institute Common Toxicity Criteria for Adverse events (CTCAE) version 4).
- Rate of completion of cancer treatment as planned (defined as completing initially planned chemotherapy course without later modifications or early discontinuation).

Secondary outcomes:

- Treatment modifications (delays and/or dose reductions and/or drug omissions).
- Early treatment discontinuation.
- Dose escalations.
- Death at 6 months.

Completing treatment as planned was chosen as a coprimary outcome because of the causal hypothesis of impact on disease outcomes, plus observational work in the control group identified that some patients have treatment modified/stopped for lower grade toxicities (Kalsi *et al*, 2014a). Patients receiving neoadjuvant and adjuvant chemotherapy had only one of these schedules assessed for toxicity (closest to recruitment date) to avoid contamination of chemotherapy toxicity by postoperative side effects. Follow-up was for 6 months, or for those who died before this, up to the point they died. The types and number of interventions resulting from CGA were evaluated to answer the secondary aim.

Statistical analysis. Univariate associations were identified using independent *T*-test for comparing means, χ^2 or Fisher's exact test for comparing categorical data. Confounder bias was minimised with logistic regression by adjusting for age plus other relevant differences between the groups (comorbidity, metastatic disease, chemotherapy dose reduction at the outset) in bivariate and multivariate analysis.

For clinical service logistical reasons, the intervention targeted gastrointestinal (GI) and urology patients, thus the range of tumour type was broader in the control. There is no widely accepted method to group different tumour types together for the purpose of statistical analysis; therefore, to ensure outcome

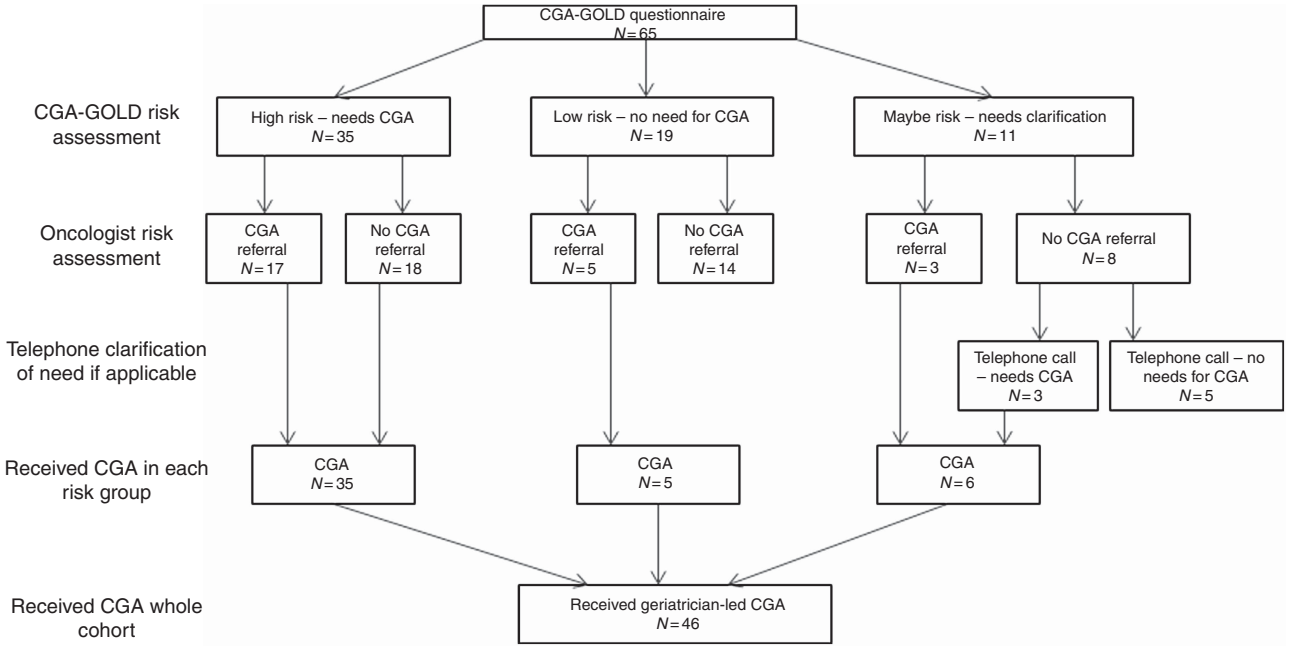

Figure 1. Risk assessment pathway used for identifying those requiring CGA in the intervention cohort.

differences were not related to tumour type, the largest single homogenous tumour group (GI) was examined separately.

RESULTS

A total of 135 participants (70 control, 65 intervention) were included with 33 control and 41 intervention participants in the GI subgroup.

Demographic, cancer, treatments, comorbidities and CGA characteristics. Table 1 compares patient and cancer-related characteristics. The control and intervention cohorts were largely well matched except for comorbid burden, metastatic disease and initial dose reductions at the outset (adjusted for in the later analysis). Thirty different chemotherapy regimens were given across the two cohorts. There were no differences in types of comorbidities and CGA characteristics, except for more diabetes (27.7% *vs* 13.2%, $P=0.038$) and polypharmacy (50.8% *vs* 31.7%, $P=0.029$) in the intervention cohort and more difficulties with family and social activities in the control group (Table 2).

Interventions. Following risk assessment, CGA was required for 70.7% (46/65) of intervention subjects, with 97.8% requiring ≥ 1 intervention plan. The mean number of CGA interventions per patient was 6.2 ± 2.6, median 6 and range 0–15. Nineteen low-risk patients were not seen for CGA, but 36.8% (7/19) required a total of 16 interventions arranged, mainly for fatigue (6), nutrition (4) and anaemia (4). A total of 299 intervention plans were made for the intervention cohort (see Table 3).

Outcomes and toxicity characteristics. The most common grade 3+ toxicities are summarised in Table 4. Outcomes were adjusted for differences between cohorts (age, comorbidity, metastatic disease and initial dose reductions). There was a nonsignificant trend for a lower grade 3+ toxicity rate in the intervention cohort (43.8% *vs* 52.9%, $P=0.292$; Table 5). More participants in the intervention group completed treatment as planned (33.8% *vs* 11.4%, odds ratio (OR) 4.14, $P=0.006$) and fewer required treatment modifications (43.1% *vs* 68.6%, OR 0.34, $P=0.006$) after adjustment for confounders (Table 5). Similar positive outcomes were observed in the GI subgroup. Intervention participants had a nonsignificant trend towards fewer discontinuing treatment early (40.0% *vs* 51.4%, OR 0.63, $P=0.183$). There were no differences in

Table 1. Patient, cancer and treatment characteristics

	Whole cohort			GI subgroup		
	Control % (*N* = 70)	Intervention % (*N* = 65)	*P*-value	Control % (*N* = 33)	Intervention % (*N* = 41)	*P*-value
Age						
Mean	74.9 ± 3.8	75.8 ± 4.5	0.250	**74.2 ± 3.4**	**76.2 ± 4.8**	**0.046**
Median	74	75		73	75	
Range	70–86	70–90		70–82	70–90	
Sex and ethnicity						
Male	50.0% (35/70)	60.0% (39/65)	0.243	63.6% (21/33)	51.2% (21/41)	0.284
Caucasian	88.1% (59/67)	82.5% (52/63)	0.373	84.4% (27/32)	82.1% (32/39)	0.795
Performance status						
PS 0–1	73.5% (50/68)	83.3 (50/60)	0.181	84.4% (27/32)	89.7% (35/39)	0.722
PS 2–3	26.5% (18/68)	16.7 (10/60)		15.6% (5/32)	10.3% (4/39)	
Cancer type						
GI cancer	47.1% (33/70)	63.1% (41/65)	0.063	100% (33/33)	100% (41/41)	NA
Other cancer	52.9% (37/70)	36.9% (24/65)		0	0	
Cancer stage						
Non-metastatic	**40.0% (28/70)**	**56.9% (37/65)**	**0.049**	51.5% (17/33)	56.1% (23/41)	0.694
Metastatic	**60.0% (42/70)**	**43.1% (28/65)**		48.5% (16/33)	43.9% (18/41)	
Treatment intent						
Curative/neoadjuvant/adjuvant	40.0% (28/70)	50.8% (33/65)	0.209	54.5% (18/33)	61.0% (25/41)	0.577
Palliative	60.0% (42/70)	49.2% (32/65)		45.5% (15/33)	39.0% (16/41)	
Number of chemoagents						
Monochemotherapy	41.4% (29/70)	36.9% (24/65)	0.592	39.4% (13/33)	31.7% (13/41)	0.491
Polychemotherapy	58.6% (41/70)	63.1% (41/65)		60.6% (20/33)	68.3% (28/41)	
Other chemotherapy characteristics						
Mean cycles delivered (range)	3.8 ± 2.8 (range 1–12)	4.2 ± 2.6 (range 1–12)	0.446	4.0 ± 3.6	4.1 ± 2.7	0.903
Median cycles delivered	3	4		3	4	
With RT	18.6% (13/70)	10.8% (7/65)	0.202	30.3% (10/33)	17.1% (7/41)	0.179
Reduced dose at outset	**20.0% (14/70)**	**40.0% (26/65)**	**0.011**	18.2% (6/33)	36.6% (15/41)	0.081
Mean % dose reduction at the outset where applicable	25.4 ± 10.3	24.3 ± 7.9	0.730	21.7 ± 7.3	25.5 ± 8.6	0.391
Median % dose reduction at the outset where applicable	25	25		25	25	
GCSF at outset	4.3% (3/70)	6.2% (4/65)	0.711	3.0% (1/33)	0	0.446
Comorbidities						
Mean	**2.9 ± 1.8**	**3.9 ± 2.1**	**0.004**	2.9 ± 1.7	3.9 ± 2.3	0.061
Median	3.0	4.0		3.00	4.00	
Range	0–8	0–10		0–8	0–10	

Abbreviations: GCSF, granulocyte-colony-stimulating factor; GI = gastrointestinal; NA = not applicable; PS = performance status; RT = radiotherapy. Note: All percentages are calculated excluding missing data. Bold highlights those numbers reaching statistical significance for differences between the control and intervention groups.

Table 2. Types of comorbidities and CGA characteristics comparison between cohorts

	Whole cohort			GI subgroup		
	Control % (*N* = 70)	Intervention % (*N* = 65)	*P*-value	Control % (*N* = 33)	Intervention % (*N* = 41)	*P*-value
Cardiac (including IHD, valve disease, arrhythmia, CCF)	27.9 (19/68)	26.2 (17/65)	0.817	29.0 (9/31)	24.4 (10/41)	0.658
IHD	10.3 (7/68)	15.4 (10/65)	0.379	12.9 (4/31)	17.1 (7/41)	0.747
Arrhythmia	16.2 (11/68)	12.3 (8/65)	0.524	12.9 (4/31)	7.3 (3/41)	0.454
Hypercholesterolaemia	23.5 (16/68)	24.6 (16/65)	0.884	19.4 (6/31)	19.5 (8/41)	0.987
Hypertension	47.1 (32/68)	50.8 (33/65)	0.669	54.8 (17/31)	51.2 (21/41)	0.761
Stoke	8.8 (6/68)	4.6 (3/65)	0.493	3.2 (1/31)	4.9 (2/41)	1.000
Non-stroke neurological	7.4 (5/68)	10.8 (7/65)	0.492	6.5 (2/31)	7.3 (3/41)	1.000
Vascular disease	7.4 (5/68)	7.7 (5/65)	1.000	9.7 (3/31)	9.8 (4/41)	1.000
DM/glucose intolerance	**13.2 (9/68)**	**27.7 (18/65)**	**0.038**	9.7 (3/31)	24.4 (10/41)	0.108
Respiratory disease	22.1 (15/68)	15.4 (10/65)	0.325	22.6 (7/31)	12.2 (5/41)	0.242
CKD	8.8 (6/68)	6.2 (4/65)	0.745	6.5 (2/31)	7.3 (3/41)	1.000
MSK	25.0 (17/68)	30.8 (20/65)	0.458	19.4 (6/31)	34.1 (14/41)	0.165
GI disease	11.8 (8/68)	18.5 (12/65)	0.280	9.7 (3/31)	19.5 (8/41)	0.331
Psychiatry	1.5 (1/68)	9.2 (6/65)	0.059	0	7.3 (3/41)	0.254
Cognitive impairment	7.6 (5/66)	6.5 (4/62)	1.000	10.0 (3/30)	7.9 (3/38)	1.000
Delirium history	10.4 (7/67)	4.9 (3/61)	0.330	6.7 (2/30)	5.1 (2/39)	1.000
Depression	7.6 (5/66)	11.5 (7/61)	0.453	3.3 (1/30)	7.9 (3/38)	0.624
Falls	8.8 (6/68)	15.4 (10/65)	0.245	3.2 (1/1)	9.8 (4/41)	0.382
Visual impairment	10.4 (7/67)	14.3 (9/63)	0.506	16.1 (5/31)	15.0 (6/40)	1.000
Hearing impairment	4.4 (3/68)	13.8 (9/65)	0.058	3.2 (1/31)	12.2 (5/41)	0.227
Osteoporosis	5.9 (4/68)	13.8 (9/65)	0.122	6.5 (2/31)	19.5 (8/41)	0.171
Urinary incontinence	19.4 (13/67)	17.5 (11/63)	0.775	9.7 (3/31)	17.5 (7/40)	0.496
Bowel difficulty	20.9 (14/67)	16.1 (10/62)	0.487	16.1 (5/31)	17.9 (7/39)	0.841
Weight loss	58.2 (39/67)	56.5 (35/62)	0.840	45.2 (14/31)	60.5 (23/38)	0.203
ADL dependency	16.2 (11/68)	23.1 (15/65)	0.316	16.1 (5/31)	19.5 (8/41)	0.712
iADL dependency	29.9 (20/67)	20.3 (13/64)	0.209	30.0 (9/30)	12.5 (5/40)	0.070
Poor mobility	13.6 (9/66)	14.8 (9/61)	0.857	6.7 (2/30)	10.5 (4/38)	0.687
Difficulty with exercise	50.0 (34/68)	47.5 (29/61)	0.780	32.3 (10/31)	43.6 (17/39)	0.333
Lives alone	35.3 (24/68)	23.1 (15/65)	0.122	35.5 (11/31)	24.4 (10/41)	0.305
Difficulty with family life	**23.1 (15/65)**	**8.1 (5/62)**	**0.020**	10.3 (3/29)	5.1 (2/39)	0.644
Difficulty with social activities	**37.3 (25/67)**	**19.4 (12/62)**	**0.024**	23.3 (7/30)	15.4 (6/39)	0.403
No care available	13.4 (9/67)	4.8 (3/63)	0.088	9.7 (3/31)	5.1 (2/39)	0.649
No emotional support	0	1.5 (1/65)	0.489	0	2.4 (1/41)	1.000
Limiting pain	12.1 (8/66)	18.0 (11/61)	0.351	17.2 (5/29)	15.4 (6/39)	1.000
Sleep difficulty	14.7 (10/68)	27.4 (17/62)	0.074	19.4 (6/31)	17.9 (7/39)	0.881
Polypharmacy (5+)	**31.7 (20/63)**	**50.8 (33/65)**	**0.029**	32.1 (9/28)	48.8 (20/41)	0.169
Admitted	61.8 (42/68)	53.8 (35/65)	0.355	51.6 (16/31)	43.9 (18/41)	0.516

Abbreviations: ADL = activity of daily living; CCF = congestive cardiac failure; CGA = comprehensive geriatric assessment; CKD = chronic kidney disease; DM = diabetes mellitus; GI = gastrointestinal; iADL = instrumental activities of daily living; IHD = ischaemic heart disease; MSK = musculoskeletal. Note: All percentages are calculated excluding missing data. Bold highlights those numbers reaching statistical significance for differences between the control and intervention groups.

all-cause death rates at 6 months (20.0% control, 15.4% intervention, $P = 0.483$).

DISCUSSION

This comparative study demonstrated that geriatrician-delivered CGA was associated with better outcomes for older people undergoing chemotherapy. More intervention participants completed treatment as planned and required fewer treatment modifications. There was a nonsignificant trend for fewer in the intervention group to develop grade 3+ toxicity. Although this did not reach statistical significance (possibly relating to small sample size), the observed differences were sufficient to warrant further investigation in future larger studies. To detect a 10% difference in grade 3+ toxicity at 80% power, a sample size of 305 in each group would be required.

The CGA-GOLD questionnaire and referrals to the geriatrician were used as risk assessment tools to identify those needing CGA. In a previous related work, CGA-GOLD demonstrated feasibility with a mean completion time of 11.7 min, completion without assistance in 86.3% (Kalsi *et al*, 2013a) and good inter-rater

Table 3. Interventions to the intervention cohort

Intervention domain	Examples of intervention plans (below are examples, intervention plans not restricted to the below)	Intervention group % (*N* = 65)
Fatigue	Investigation and/or treatment of thyroid disease, anaemia, treatment of poor nutrition, mood/anxiety, provision of advice/information on coping strategies, adjusting contributing medications	49.2 (32/65)
Anaemia	Treatment of iron/B12/folate deficiency anaemia (including with intravenous iron, oral supplements and blood transfusions)	43.1 (28/65)
Nutrition	Dietitian referral, provision of nutritional supplements, plan for needed dentures, referral for home meal delivery, appetite stimulants	36.9 (24/65)
Plan in response to an abnormal test	Replacement of vitamins (e.g. vitamin D), medication changes in response to electrolyte abnormalities (e.g. diuretics and low sodium), arranging endoscopy in unexplained significant iron deficiency	35.4 (23/65)
Bladder	Investigation and management of incontinence – for example, provision of pelvic floor exercises, bladder retraining exercise, double voiding technique. Adjusting modifiable factors (e.g. drugs, lifestyle exacerbators, atrophic vaginitis, retention), medical treatment of detrusor instability Treatment of benign prostatic hypertrophy, treatment of urine infections, arranging trial without catheters	32.3 (21/65)
Cardiac	Optimisation of IHD medications where relevant (e.g. aspirin, increasing anti-anginals), pacemaker organisation, investigation of previously undiagnosed cardiac disease (e.g. echo, stress test, 24 h tape)	24.6 (16/65)
Pain	Alteration to analgesia to optimise pain control	23.1 (15/65)
Diabetes intervention	Adaptation to diabetic medications, pre-emptive planning for changes to medications during treatment (e.g. plan for high glucose when steroids, or low glucose if expected reduced oral intake), arrange monitoring (general practice, district or diabetic nurse), arranging needed equipment, for example, blood glucose monitoring machine, arranging chiropody for diabetic foot risk	21.5 (14/65)
Medication change	Reduction in unnecessary polypharmacy, adjusting antihypertensives in over/undertreated, adjusting β-blockers in overtreated	18.5 (12/65)
HTN	Adjusting antihypertensives (reducing or increasing). Pre-emptive planning for low blood pressure during chemotherapy	16.9 (11/65)
Bowels	Treatment of constipation, provision of anal sphincter exercises in faecal incontinence, management of diarrhoea	16.9 (11/65)
Social	Referral to social services, district nurse referrals, occupational therapy assessment for equipment needs, provision of information on transport support and referrals for financial support	15.4 (10/65)
Postural hypotension	Adjustment to causative medications, lifestyle advice (increase fluids, reduce caffeine), pre-emptive plans for exacerbating toxicities (e.g. diarrhoea)	13.8 (9/65)
Renal	Reduction in renal toxic medications if required (e.g diuretics), vitamin D replacement, measurement of urine:creatinine ratio if relevant	12.3 (8/65)
MSK	Management of arthritis pain (medications, TENS), treatment of osteoporosis	12.3 (8/65)
Falls	Identify and management plan for contributing factors (e.g. adapt medications, organise any necessary investigations (e.g. 24 h tape), physiotherapy referrals for strength and balance training, occupational therapy referrals for equipment needs or home falls risk assessment	12.3 (8/65)
Mood	Adjusting/starting antidepressants, referral for counselling	10.8 (7/65)
Referral to specialist	Referral to cardiologist if significant reversible ischaemia requiring immediate treatment, dermatology for treatment of basal cell carcinoma, palliative care referrals	10.8 (7/65)
Memory	Memory clinic referral if significant cognitive impairment, assisting with mental capacity assessment, identifying and treating any exacerbating factors (e.g. mood, medications), identifying delirium risk and pre-emptive strategies to manage delirium ± reduce risk	9.2 (6/65)
Respiratory	Adapting relevant medications (e.g. inhalers, treatment of exacerbations), organising any needed investigations (e.g. spirometry), smoking cessation referral and nicotine replacement, referral for pulmonary rehabilitation	9.2 (6/65)
Hearing	Referral to audiology, treatment of significant wax ± referral for microsuctioning	6.2 (4/65)
Peripheral neuropathy	Treatment of contributors (B12 deficiency)	6.2 (4/65)
Sleep	Advice around lifestyle contributors (sleep hygiene, caffeine), adjusting exacerbating medications (e.g. diuretics), management of other contributors, for example, mood	3.1 (2/65)
Vision	Referral for visual aids/assessment	4.6 (3/65)

Abbreviations: HTN = hypertension; IHD = ischaemic heart disease; MSK = musculoskeletal; TENS = transcutaneous electrical nerve stimulation. Note: All percentages are calculated excluding missing data.

reliability (κ 0.80) for risk assessment (Kalsi *et al*, 2014b). Other studies have also demonstrated feasibility of self-reported screening tools; a US study showed completion rates of 98% and mean completion time of 15 min (Hurria *et al*, 2007).

Nearly 300 intervention plans were made to investigate/modify/support comorbidities and CGA needs for the 65 intervention participants. Intervention plans were made for comorbidities (e.g. cardiac disease, diabetes), CGA issues (e.g. bladder, nutrition, medication reviews), symptoms (e.g. fatigue, pain) and in response to abnormal tests, a finding consistent with others (Caillet *et al*, 2011; Chaibi *et al*, 2011). A French study demonstrated that geriatrician-delivered CGA led to a number of interventions, including 69.9% nutritional, 30.7% medication changes and further investigations for 54.9% (Caillet *et al*, 2011). A chemotherapy-specific study demonstrated that 122 patients required 227 intervention plans in five target intervention domains (nutrition, depression, cognition, polypharmacy and social interventions); 81 required actions for $\geq$2 of the target domains (Chaibi *et al*, 2011).

Table 4. Prevalence of most common grade 3+ toxicities

	Control % (*N* = 70)	Intervention % (*N* = 65)	*P*-value
Neutropenia	20.0 (14/70)	14.1 (9/64)	0.363
Fatigue	12.5 (8/64)	12.9 (8/62)	0.946
Anaemia	14.3 (10/70)	4.7 (3/64)	0.061
Lymphopenia	12.9 (9/70)	7.8 (5/64)	0.340
Infection	8.6 (6/70)	3.1 (2/64)	0.278
Dehydration	7.1 (5/70)	3.1 (2/64)	0.444
Febrile neutropenia	5.7 (4/70)	4.7 (3/64)	1.000
Thrombocytopenia	4.3 (3/70)	4.7 (3/64)	1.000
Nausea	4.3 (3/70)	3.1 (2/64)	1.000
Diarrhoea	4.5 (3/67)	1.6 (1/64)	0.620
Peripheral neuropathy	4.3 (3/70)	0	0.246

Note: All percentages are calculated excluding missing data.

To the authors knowledge, this is the first study examining the impact of geriatrician-delivered CGA interventions to optimise chemotherapy tolerance and reduce toxicity in older people with cancer. Despite the robust evidence base for CGA in other settings (Stuck *et al*, 1993; Elliot *et al*, 1996; Vidan *et al*, 2005; Harari *et al*, 2007; Ellis *et al*, 2011a, b; Gonzalez Montalvo *et al*, 2011), this has been little applied to the chemotherapy setting. Studies investigating chemotherapy tolerance and toxicity have focussed on GA screening tools rather than CGA. GA screening tools have demonstrated utility in predicting chemotherapy toxicity, although studies vary as to which particular GA domains are associated with toxicity (Extermann *et al*, 2011; Hurria *et al*, 2011; Hamaker *et al*, 2012), and others have demonstrated no associations (Hamaker *et al*, 2012).

The findings of this study are generalisable to a variety of tumour types and chemotherapy regimens with/without radiotherapy. Our population was well matched to those previously reported indicated by the similar grade 3+ toxicity rate in our control group to the existing literature (Hurria *et al*, 2011). The population studied included inner city and suburban residents and was generalisable within NHS England.

This study, however, has limitations. The small sample size may have contributed to nonsignificant results. As a comparative cohort study, there is the potential for bias which may be minimised with a randomised controlled trial design. However, differences between the groups were identified, examined and adjusted for statistically.

There was a higher number of comorbidities in the intervention group which may represent increased detection by the geriatrician. However, the corresponding higher polypharmacy would indicate that this group was genuinely more comorbid yet still had better outcomes. There was also a difference in the spread of tumour types between the groups. However, the improved outcomes in the intervention group held true in the homogenous GI subgroup. More patients in the intervention group also started at a reduced dose at the outset that may reflect their higher comorbid burden. The most common documented reason for initial dose reductions in the intervention group was comorbidity. It may also reflect the influence of CGA on decision making, facilitating individualised treatment plans. Comprehensive geriatric assessment demonstrated influence on decision making in 62.5% in previous work related to this intervention study (Kalsi *et al*, 2013b). Similarly, CGA has demonstrated influence on decision making in 20.8–49% in France (Caillet *et al*, 2011; Chaibi *et al*, 2011).

The higher reduced dose at the outset in the intervention group did not adversely affect disease control at 6 months (identified in further analysis). In addition, tolerance and toxicity outcomes remained statistically significant after adjustment for this initial dose reduction. Adapted regimens have been shown not to adversely affect outcomes in other studies. However, the follow-up period for this study was 6 months. Longer follow-up would be required to evaluate the longer-term impact of these initial dose reductions on disease control.

This study also included a number of different chemotherapy regimens. Chemotherapy type was not adjusted for, thus the results should be interpreted with caution. There is no standard accepted method for adjusting for chemotherapy type. The MAX2 index has been previously developed for this purpose (Extermann *et al*, 2002) and validated in trial participants (Extermann *et al*, 2004). However, we did not apply the MAX2 to this study for a number of reasons including (a) differences in definition of severe toxicity, (b) the validation study used clinical trials participants only, thus likely 'fitter' than the more heterogeneous cohort of this study and (c) the validation study included fewer tumour types, metastatic/advanced disease only and fewer treatment regimens, and thus differed from our study population. However, in our study we identified there were no differences between the groups in terms of mono- and polychemotherapy between the groups. In addition, the homogenous GI subgroup analysis served both to evaluate whether the outcomes held true not only to tumour type but also in a group who would thus also better matched in terms of the types of chemotherapy regimens received. The positive outcomes remained true in this subgroup analysis.

There is a need for clinical practice to evolve in response to the changing needs of the population presenting to cancer services. Issues identified through CGA are potentially modifiable through intervention. Clinical trials evaluating the impact of CGA interventions on chemotherapy tolerance are needed. Oncology studies should shift their focus from GA tools towards the interventional CGA clinical process, as highlighted in the recent SIOG consensus (Wildiers *et al*, 2014), and this study could serve to inform future statistical power.

This study would also add support to the recommendations from the recent UK Department of Health report 'Cancer Services Coming of Age' (Department of Health, 2012b)) to medically optimise older people for cancer treatment. This, in part, could be delivered by increasing geriatrics skills within oncology training. In some areas of the world curricula have developed (Cohen, 1997; Muss *et al*, 2005), whereas others are yet to make curricula change with resulting lack of trainee confidence in managing older people (Kalsi *et al*, 2013c).

The service model of CGA delivered via geriatrician liaison was evaluated. Although hospitals in the United Kingdom predominantly have both specialists working in the same hospital, formal geriatric-oncology liaison services are rarely resourced. Comprehensive geriatric assessment may not need to be delivered by geriatricians. Protocolised intervention plans facilitated remotely by geriatricians but delivered by nurses (McCorkle *et al*, 2000) or other clinicians may be effective. However, the UK Macmillan/Department of Health Older Persons Pilot (of which this was one pilot site) demonstrated that geriatrician liaison was the most effective way of delivering CGA (Department of Health, 2012b)). Furthermore, the complexity of some older people and the interaction between comorbidity, wider issues (falls, continence, cognition) and function may be better managed by geriatricians, as demonstrated in this study as well as in other clinical settings (Stuck *et al*, 1993; Elliot *et al*, 1996; Vidan *et al*, 2005; Harari *et al*, 2007; Ellis *et al*, 2011a,b; Gonzalez Montalvo *et al*, 2011). This study provides some support to the value of developing and sustaining such services for older people with cancer.

Geriatrician input is being delivered in a few specialist geriatric oncology centres across the world (e.g. France, United States). It is perhaps time for this practice to become more widespread, with more consistent inclusion of the geriatrician in the cancer multidisciplinary team. The focus has to be on improving patient

Table 5. Toxicity and tolerance outcomes (univariate, bivariate and multivariate analysis)

	Whole cohort outcomes				GI subgroup outcomes			
	Control % (*N* = 70)	Intervention % (*N* = 65)	Odds ratio (95% CI)	*P*-value	Control % (*N* = 33)	Intervention % (*N* = 41)	Odds ratio (95% CI)	*P*-value
Analysis	**Grade 3+ toxicity**				**Grade 3+ toxicity**			
Univariate	52.9 (37/70)	43.8 (28/64)	0.69 (0.35–1.37)	0.292	48.5 (16/33)	39.0 (16/41)	0.68 (0.27–1.72)	0.414
Bivariate[a]								
Age			0.68 (0.34–1.36)	0.276			0.65 (0.25–1.69)	0.378
Comorbidity			0.68 (0.34–1.38)	0.288			0.61 (0.23–1.63)	0.326
Reduced start dose			0.76 (0.38–1.52)	0.431			0.82 (0.31–2.15)	0.686
Metastatic disease			0.61 (0.30–1.24)	0.173			0.61 (0.23–1.63)	0.324
Multivariate[b]			0.62 (0.29–1.32)	0.217			0.55 (0.18–1.64)	0.281
	Completion of treatment as planned				**Completion of treatment as planned**			
Univariate	11.4% (8/70)	33.8 (22/65)	3.97 (1.62–9.73)	0.002	18.2 (6/33)	43.9 (18/41)	3.52 (1.20–10.35)	0.019
Bivariate[a]								
Age			4.00 (1.62–9.86)	0.003			4.21 (1.37–12.95)	0.012
Comorbidity			4.47 (1.71–11.66)	0.002			4.29 (1.34–13.78)	0.014
Reduced start dose			4.45 (1.76–11.21)	0.002			3.95 (1.30–12.01)	0.016
Metastatic disease			3.48 (1.38–8.75)	0.008			3.71 (1.20–11.45)	0.023
Multivariate[b]			4.14 (1.50–11.42)	0.006			5.00 (1.42–17.69)	0.012
	Treatment modification				**Treatment modification**			
Univariate	68.6 (48/70)	43.1 (28/65)	0.35 (0.17–0.70)	0.003	69.7 (23/33)	34.1 (14/41)	0.23 (0.08–0.60)	0.002
Bivariate[a]								
Age			0.36 (0.18–0.74)	0.005			0.24 (0.09–0.65)	0.005
Comorbidity			0.33 (0.16–0.69)	0.003			0.18 (0.06–0.51)	0.001
Reduced start dose			0.36 (0.17–0.73)	0.005			0.24 (0.09–0.65)	0.005
Metastatic disease			0.35 (0.17–0.71)	0.004			0.23 (0.09–0.61)	0.003
Multivariate[b]			0.34 (0.16–0.73)	0.006			0.19 (0.07–0.58)	0.003
	Early discontinuation				**Early discontinuation**			
Univariate	51.4 (36/70)	40.0 (26/65)	0.63 (0.32–1.25)	0.183	36.4 (12/33)	36.6 (15/41)	1.01 (0.39–2.62)	0.984
Bivariate[a]								
Age			0.59 (0.30–1.18)	0.138			0.86 (0.32–2.32)	0.763
Comorbidity			0.60 (0.30–1.23)	0.163			1.01 (0.37–2.75)	0.979
Reduced start dose			0.56 (0.28–1.15)	0.113			0.83 (0.31–2.26)	0.719
Metastatic disease			0.75 (0.36–1.53)	0.423			1.10 (0.39–3.07)	0.858
Multivariate[b]			0.67 (0.31–1.45)	0.305			0.93 (0.30–2.94)	0.907
	Dose escalated				**Dose escalated**			
Univariate[c]	0	4.6 (3/65)	[c]	0.109	0	2.4 (1/41)	[c]	1.000
	Deaths at 6 months				**Deaths at 6 months**			
Univariate	20.0 (14/70)	15.4 (10/65)	0.73 (0.30–1.78)	0.483	21.2 (7/33)	12.2 (5/41)	0.52 (0.15–1.81)	0.296
Bivariate[a]								
Age			0.68 (0.27–1.68)	0.401			0.47 (0.13–1.74)	0.258
Comorbidity			0.69 (0.27–1.77)	0.440			0.53 (0.14–2.04)	0.358
Reduced start dose			0.68 (0.27–1.71)	0.415			0.47 (0.13–1.71)	0.252
Metastatic disease			0.87 (0.35–2.20)	0.773			0.53 (0.14–1.93)	0.333
Multivariate[b]			0.86 (0.31–2.37)	0.765			0.59 (0.13–2.64)	0.493

All percentages are calculated excluding missing data.
[a]Bivariate adjusted separately for each covariant tabled.
[b]Multivariate adjusted for age, comorbidity, metastatic disease and reduced starting dose together.
[c]Numbers too small for further analysis.

factors to improve chemotherapy tolerance and clinical outcomes for older people with cancer.

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