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The impact of low-grade toxicity in older people with cancer undergoing chemotherapy

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Background: Significant toxicity in chemotherapy trials is usually defined as grade $\geqslant 3$. In clinical practice, however, multiple lower grade toxicities are often considered meaningful. The purpose of this observational cohort study was to identify which level of toxicity triggers treatment modification and early discontinuation of chemotherapy in older people.

Methods: Patients aged 65+ were recruited in a central London hospital. A total of 108 patients were recruited at the start of new chemotherapy treatment between October 2010 and July 2012.

Results: Mean age was 72.1 ± 5 years, median 72 and range 65–86 years. Of the patients, 50.9% (55) were male with gastrointestinal (49), gynaecological (18), lung (15) and other cancers (26). Chemotherapy was palliative in 59.3% (64/108), curative/ neoadjuvant/ adjuvant in the others. Mean number of cycles completed was 4.2 ± 3. Treatment modifications due to toxicity occurred in 60 (55.6%) patients, 35% (21/60) of whom had no greater than grade 2 toxicity. Early treatment discontinuation because of toxicity occurred in 23 patients (21.3%), 39.1% (9/23) of whom had no greater than grade 2 toxicity.

Conclusions: Many older patients did not complete treatment as planned. Treatment was modified/discontinued even for one or two low-grade toxicities. Further work is required to clarify whether low-grade toxicity has a greater clinical impact in older people, or whether clinicians have a lower threshold for modifying/discontinuing treatment in older people.

Delivering chemotherapy to older people can be a challenge for clinicians. Older people are living longer with a variety of comorbidities of differing severities, functional deficits and degrees of 'frailty'. Consequently, decision-making in respect to chemotherapy can be complex. The decision includes evaluating who is robust enough to tolerate chemotherapy, tolerate full dose treatment and/or to continue through chemotherapy treatment without modifications. A judgement needs to be made as to whether the patient will actually gain benefit from the treatment. In the absence of a unifying criteria beyond performance status (PS)

to assist decision-making, a subjective decision is made by the individual clinician using the available information.

There are often concerns of increased risk of toxicity in older people (Lichtman *et al*, 2007; Wedding *et al*, 2007). Some studies indicate increased toxicity with age (Stein *et al*, 1995; Tsalic *et al*, 2003; Jantunen *et al*, 2006). However, these studies did not control for comorbidities that may equally affect tolerance to chemotherapy. This raises the concern that comorbidity and not age is the contributing risk factor (Wedding *et al*, 2007). The distinction is essential as comorbidity is potentially modifiable (e.g., renal

impairment, hypertension etc.) and sometimes reversible (e.g., incontinence). Conversely, several studies (clinical trials and real life clinical practice analyses) have shown that older people have equal benefit and tolerate treatment as well as younger people (Giovanazzi-Bannon et al, 1994; Sargent et al, 2001; Garcia-Suarez et al, 2003; Goldberg et al, 2006; Mitry and Rougier, 2009; Park et al, 2012). A pooled reanalysis of large clinical trials has shown that older patients received the same benefit as younger patients without an increase in toxicity (Giovanazzi-Bannon et al, 1994). However, these pooled analyses did not report the selection criteria for the clinical trials, nor important characteristics (e.g., comorbidities) which would enable a judgement to be made regarding the relevance of these results to clinical practice. Older people included in clinical trials are likely to have a better PS and fewer comorbidities than the whole population of older people with cancer, and thus are not representative of the heterogeneous group seen in clinical practice, about which there is little published literature.

The paucity of clinical information makes it harder to make evidence-based decisions around the management of chemotherapy in older people (Lichtman et al, 2007; Wu and Goldberg, 2013). Older people are underrepresented in clinical trials (Yee et al, 2003). There are a number of factors contributing to this including the exclusion of older people from clinical trials, either because of study protocols excluding comorbidities common in older people or by upper age limits (Droz et al, 2008). In addition, even where eligible, oncologists have been observed to be less likely to include older people in trials (Benson et al, 1991). The risk/benefit decision is consequently often influenced by either observational study evidence, subgroup analyses and/or by the previous experience of the individual clinician (Wu and Goldberg, 2013). There may be less clinical confidence in assessing this risk in older people – this has been observed by oncologists in training (Kalsi et al, 2013).

In addition, the analysis and reporting of toxicity within clinical trials is more focussed on severe toxicity usually defined as National Cancer Institute Common Toxicity Criteria (NCI-CTCAE version 4.0) grade 3–4. In clinical practice, the occurrence of multiple lower grade toxicities is often considered clinically relevant and may result in changes in clinical decision-making. We hypothesise that multiple low-grade toxicities may be a common reason for treatment modification/discontinuation in older people. The purpose of this observational cohort study was to:

1. Identify which grade(s) of toxicity (and how many) trigger (i) treatment modification (defined as dose reductions, delays or drug omissions) and (ii) early discontinuation of treatment.
2. Identify the factors associated with modifications/discontinuation made because of low-grade toxicity.

MATERIALS AND METHODS

Study design and setting. This prospective observational cohort study was set in a London teaching hospital between February 2010 and October 2012. A total of 516 patients aged 65 + undergoing treatment for cancer (chemotherapy, radiotherapy, surgery, watchful waiting) were recruited to the overall study with the aim of identifying comorbidity and comprehensive geriatric assessment (CGA) characteristics that are associated with poorer treatment tolerance (Ethics approval: LREC 09H71865). The primary outcomes of interest for the overall study included toxicities, surgical complications, treatment modifications/non-completion and disease control/progression. This study examines a subgroup of 108 patients who were recruited at the start of new chemotherapy treatment (recruited between October 2010 and

July 2012). Patients excluded from this analysis either received a non-chemotherapy treatment modality or were not recruited at the start of chemotherapy. All participants provided consent and were asked to complete a baseline questionnaire (CGA-GOLD) (available in the online Supplementary Material). This included self-reported comorbidities and all CGA domains (e.g., falls, incontinence, delirium, psychosocial, instrumental and basic activities of daily living) (Balducci, 2003; Chen et al, 2003; Minisini et al, 2004; Terret et al, 2004; Extermann et al, 2005; Gosney, 2005; Hurria et al, 2005, 2007; Mohile et al, 2007; Rodin and Mohile, 2007; Girre et al, 2008), quality of life (EORTC QLQ-C30) (Aaronson et al, 1993) and additional questions from our user consultation.

Self-reported CGA has been feasibly conducted in cancer outpatients in the US and Europe (Ingram et al, 2002; Hurria et al, 2005; Girre et al, 2008; Marenco et al, 2008). The feasibility and utility as well as validity and reliability of CGA-GOLD has been previously reported (Kalsi et al, 2013, 2014). Oncologists were blinded to the questionnaire responses and so consented patients received unbiased care according to standard clinical management.

Subjects. Potential participants were identified from oncology clinic lists and chemotherapy day unit lists on the hospital electronic record system. Patients were mailed study information and given a minimum of 48 h to consider participation prior to consent. Questionnaires were returned by participants by post.

Patients aged 65 + with cancer recruited prior or within the first cycle of chemotherapy were included in the analysis. Patients receiving concomitant radiotherapy were also included. Patients receiving both neoadjuvant and adjuvant chemotherapy only had one of these schedules assessed for toxicity (whichever was closest to the recruitment date). The rationale was to avoid contamination of the chemotherapy toxicity outcome by post-operative side effects.

Data collection. Data were collected using the hospital electronic patient records. Patient characteristics (age, comorbidities, PS) were identified from patient records. Clinical outcomes were followed up for 6 months from the first dose of chemotherapy. Toxicity data and treatment changes were identified by review of prospectively recorded oncology electronic notes and clinical letters. Reasons for treatment changes (i.e., if toxicity related) were also identified in the same way. Patients were followed up for toxicity data to the end of the treatment course, or if chemotherapy was given for longer than 6 months, toxicity follow-up ceased at 6 months to avoid skewing of data as a validated approach (Extermann et al, 2011). Toxicity during the treatment course was recorded as per the grades documented in the clinical notes entry. Where clinicians had not graded toxicity but had adequately described the toxicity, grading was assigned retrospectively using NCI-CTCAE version 4.0. Laboratory results during chemotherapy were reviewed to identify haematological toxicity and graded using NCI-CTCAE version 4.0.

Patients who were identified as having treatment modified or discontinued because of toxicity were then further examined to identify the grades of toxicities during their treatment course. Those with modifications/discontinuation who only suffered low-grade toxicity were further examined for the number of low-grade toxicities occurring in their treatment course.

Statistical analysis. Toxicity data were dichotomised to low-grade (grade 1–2) and high-grade (grade 3 +) toxicity. Participants were described as suffering low or high toxicity based on the highest recorded grade of toxicity for the individual. Predictors were also prospectively dichotomised (age: <75 vs 75 +, comorbidities: <4 vs 4 +, PS: 0–1 vs 2–3 and treatment intent: curative/adjuvant/neoadjuvant vs palliative). Associations between predictors and treatment modification and discontinuation because of low-grade

toxicity were investigated with univariate analysis using χ^2 or Fisher's exact test if the expected frequency was less than 5. SPSS version 19 statistical software package (SPSS, Inc., Chicago, IL, USA) was used for data analysis.

RESULTS

Fifty-three participants were recruited prior to the first cycle and 55 within the first cycle of chemotherapy. All 108 completed follow-up as planned. Ninety-one completed the 6-month follow-up, 17 (15.7%) to the point prior to 6 months at which they died (Figure 1).

The mean age of participants was 72.1 ± 5 years, median 72, range 65–86. Of them, 50.9% ($n = 55$) were male and 89.5% ($n = 94$) white; 82.5% were PS 0–1, 14.6% PS 2 and 2.9% PS 3. Participants had gastrointestinal (49), gynaecological (18), lung (15) and other cancers (26). More than three active comorbidities were present in 50% of the cohort. The most common comorbidities were hypertension (39.6%), cardiac disease (23.6%), musculoskeletal disease (22.6%), hypercholesteraemia (21.7%), respiratory disease (17.0%), thrombo-embolism (17.9%) and diabetes (14.2%).

Chemotherapy was palliative in 59.3% (64/108) and curative/adjuvant/neoadjuvant in 40.7% (44/108). Forty-seven different chemotherapy regimens were administered, 16.7% with concomitant radiotherapy; 76.9% (83) had full dose at the outset. Median chemotherapy cycles completed were 4, mean 4.2 ± 3, range 1–12.

Table 1 describes toxicity incidence and Table 2 describes the incidence of the most common individual toxicities by grade. Toxicity (all grades) occurred in 93.5% of participants, 50.9% with grade $3+$ and 42.6% with low grade. The most common low-grade toxicities included fatigue, nausea, diarrhoea, constipation and haematological toxicity. The number of missing toxicity data was small (0.46%).

Treatment changes due to toxicity. Treatment modification due to toxicity occurred in 60 patients, 35% (21/60) of whom had no greater than grade 2 toxicity. Of these 21, the mean number of low-grade toxicities resulting in treatment modification was 2.19 ± 1.33, 7 patients had only one grade 2 toxicity. Most common low-grade toxicity types resulting in treatment modification were fatigue (8), haematological (8), gastrointestinal (6) and infections (5).

Non-completion of treatment because of toxicity occurred in 23 patients, 39.1% (9/23) of whom had no greater than grade 2 toxicity. Of these nine, the mean number of low-grade toxicities resulting in treatment discontinuation was 1.78 ± 1.20, three had only one grade 2 toxicity, one patient only grade 1 toxicity. Most common low-grade toxicities resulting in treatment discontinuation were fatigue (5) and haematological toxicity (4). A further 24 patients did not complete treatment because of disease progression.

Factors associated with toxicity-related treatment modifications/discontinuation. Table 3 demonstrates univariate associations of age, comorbidity, PS and treatment intent with low-grade toxicity (vs high) resulting in treatment modifications and discontinuation. Low-grade toxicity triggering treatment modification was associated with a higher comorbid burden ($4+$ comorbidities), $P = 0.01$. There was no association between low-grade toxicity and age, PS or treatment intent triggering treatment modification or discontinuation.

DISCUSSION

Low-grade toxicity appears to have clinical significance in older people undergoing chemotherapy. Many older patients did not complete treatment as planned. Low-grade toxicity resulted in treatment modification for 19.4% (21/108) and treatment discontinuation for 8.3% (9/108) of the whole cohort. Treatment was modified/discontinued even for one or two low-grade toxicities. The accumulation of these low-grade toxicities appear important in determining future dosing and ongoing treatment. Fatigue and haematological toxicity were the most common low-grade toxicities impacting on treatment change.

Modifications due to low-grade toxicity was not associated with age. A number of older people were able to complete a reasonable amount of chemotherapy (median 4 cycles). Treatment modification for low-grade toxicity occurred more often in those with multiple comorbidities. This study would thus support that treatment decision-making should not be driven by chronological age and that comorbid burden appears far more relevant.

To the authors' knowledge, this is the first study specifically investigating the impact of low-grade toxicity in older people undergoing chemotherapy. Other studies in older people have been performed investigating the impact of toxicity in general on chemotherapy completion. In a study of 171 patients with small
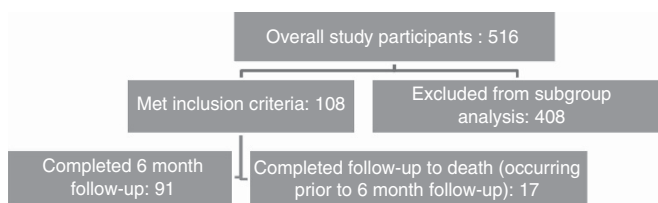

Figure 1. Results – participants.

Table 2. Incidence of most common toxicities by grade

Toxicity	Grade 1–2 % (N)	Grade 3+ % (N)
Fatigue	50.9 (55/108)	10.2 (11/108)
Nausea	37.0 (40/108)	2.8 (3/108)
Lymphocytopenia	35.2 (38/108)	11.1 (12/108)
Diarrhoea	34.2 (37/108)	4.6 (5/108)
Thrombocytopenia	25.0 (27/108)	3.7 (4/108)
Constipation	25.0 (27/108)	0 (0/108)
Peripheral neuropathy	23.1 (25/108)	3.7 (4/108)
Anaemia	19.4 (21/108)	11.1 (12/108)

Table 1. Incidence of toxicity

	All grades % (N)	Grade 1–2 % (N)	Grade 3+ % (N)
Non haematological toxicities	92.6 (100/108)	60.2 (65/108)	32.4 (35/108)
Haematological toxicity	66.7 (72/108)	37.0 (40/108)	29.6 (32/108)
Treatment modification due to toxicity	55.6 (60/108)	19.4 (21/108)	36.1 (39/108)
Treatment discontinued due to toxicity	21.3 (23/108)	8.3 (9/108)	13.0 (14/108)

Table 3. Associations with low-grade toxicity resulting in treatment modification and treatment discontinuation

	Treatment modification (N = 60)			Treatment discontinuation (N = 23)		
	Low-grade toxicity (N = 21)	High-grade toxicity (N = 39)		Low-grade toxicity (N = 9)	High-grade toxicity (N = 14)	
	% (N)	% (N)	P-value	% (N)	% (N)	P-value
Age						
<75 years	31.6 (12)	68.4 (26)	0.47	30.8 (4)	69.2 (9)	0.42
75 + years	40.9 (9)	59.1 (13)		50.0 (5)	50.0 (5)	
Comorbidity						
<4 comorbidities	**24.4 (10)**	**75.6 (31)**	**0.01**	33.3 (5)	66.7 (10)	0.66
4 + comorbidities	**57.9 (11)**	**42.1 (8)**		50.0 (4)	50.0 (4)	
Performance status (one missing data)						
PS 0–1	37.5 (18)	62.5 (30)	0.73	40.0 (6)	60.0 (9)	1.00
PS 2–3	27.3 (3)	72.7 (8)		42.9 (3)	57.1 (4)	
Treatment intent						
Curative/adjuvant/neoadjuvant	34.8 (8)	65.2 (15)	0.98	50.0 (4)	50.0 (4)	0.66
Palliative	35.1 (13)	64.9 (24)		33.3 (5)	66.7 (10)	

cell lung cancer, 117 of whom who received chemotherapy, 40 patients had a dose reduction and 56 patients did not complete treatment as planned (Fisher *et al*, 2012). Toxicity (grades not specified) was the most common reason for treatment change. Of those with dose reductions, 75% were due to haematological toxicity and 25% due to frailty/PS. Of those with early discontinuation, 56% were discontinued because of haematological toxicity, 34% non-haematological toxicity, 44% related to frailty/PS and 25% medical reasons. Another study of 108 elderly patients with a variety of cancer types also identified haematological toxicity to be associated with relative dose intensity in regression analyses (Luciani *et al*, 2006). A study of 532 patients (all ages) with a variety of tumour groups also looked at the impact of adverse drug reactions on chemotherapy completion (Llopis-Salvia *et al*, 2010). Of the 3553 chemotherapy cycles, 12.9% were not delivered as planned because of adverse drug reactions. Adverse drugs reactions caused treatment delays ⩾7 days for 307 cases, dose reductions for 91, dose omissions in 29 and treatment discontinuation in 112 cases.

This study investigates a very large but understudied population. We examined impact according to age, PS, comorbidity and treatment intent. A variety of tumour and chemotherapy types have been included in the analysis improving generalisability.

This study has limitations. The cohort is small and our sub-optimal sample size may contribute to some non-significant results. We did not study patients under the age of 65. We cannot exclude that a similar study conducted in younger patients may reveal similar findings. A high proportion of participants had PS 0–1. Future work could compare younger matched controls and/or specifically target older people with PS 2 +. Toxicity was also identified from that documented in routine clinical practice because of the limitations in size of the research team. This may risk underreporting of toxicity when compared with a clinical trial setting. These results need internal and external validation in a larger sample size to allow for appropriate multivariate analysis to more thoroughly investigate for associations.

This study has potentially significant implications. It highlights that the measure and reporting of lower grade toxicity and its impact should be considered in the design of future clinical trials, especially low-grade fatigue and haematological toxicity. This would better reflect real life clinical decision-making and would assist clinicians in making evidence-based decisions regarding the risks of a particular chemotherapy.

Key questions are also raised. Does low-grade toxicity truly have a greater clinical impact on older people? Or is there a lower threshold for modifying/discontinuing treatment in older people? If so, why? Or is treatment modified for low-grade toxicity similarly in younger people? And finally, as highlighted by the 2012 Department of Health report 'Cancer Services coming of Age' (Department of Health, 2012), it may be beneficial to medically 'optimise' older people for chemotherapy. Comorbidities and functional deficits should be thoroughly assessed and modified where possible prior to starting chemotherapy. Strategies should be sought aimed at ameliorating/optimising significant grade 2 toxicities such as fatigue and haematological toxicity (e.g., increasing the use of growth factor support, pre-treatment optimisation of anaemia).

Cancer services should consider reconfiguration of the multi-disciplinary team to include geriatricians to support the wider needs of older people. Medical and social optimisation may improve the impact of low-grade toxicity on the ability of patients to receive and complete chemotherapy as planned.

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Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)