Introduction

The Liverpool Reviews and Implementation Group (LR*i*G) conducted six individual systematic reviews to examine the effectiveness and tolerability of systemic anti-cancer therapy used to treat older people with breast, colorectal, lung, renal cell, chronic myeloid leukaemia (CML) and non-Hodgkin's lymphoma (NHL). The six individual reviews aimed to summarise relevant clinical evidence, disseminate accessible information to clinicians, and inform future clinical research priorities. The reviews primarily focussed on efficacy (e.g. overall survival, objective response), tolerability (e.g. relative dose intensity, withdrawals, and adverse events), but also collected data relating to quality of life (QoL), and the use of comprehensive geriatric assessment (CGA). A total of 490 studies were included across the six individual reviews, including evidence from 64 randomised controlled trials (RCTs). The largest review related to lung cancer (included studies, n=199) and the smallest review was for renal cell carcinoma (included studies, n=9). This paper, written by the review authors, presents a summary of the evidence relating to the reported use of CGA as described in the six reviews; the full methods and results of the individual six review publications can be accessed via the LR*i*G website (Liverpool Reviews and Implementation Group, 2016).

Historically cancer treatments have had significant negative side effects and so their use has been frequently limited to younger and fitter patients. However, newer cancer treatments have fewer side effects and come with management algorithms means they are often preventable and are easier to manage when they do occur. As a result, chronological age alone is no longer considered an appropriate measure for determining an older person's suitability for cancer treatment or for entry into a clinical trial. It is advocated by the International Society for Geriatric Oncology (SIOG) that CGA should be used in routine practice (International Society of Geriatric Oncology, 2016). CGA is a multidimensional process which involves the use of standardised measurement tools that can help to determine appropriate treatment choices for older people with cancer, to predict the side effects and potential complications of treatment, to improve patients' mental health and physical wellbeing, and to estimate survival (Hurria and Cohen, 2016).

Clinical studies often use CGA for a variety of purposes, such as to determine patient eligibility for trials or as an outcome measure to establish how well patients have responded to treatment in terms of how fit and well they are. When CGA is used appropriately it measures several domains, including functional status, comorbidity, cognitive function, psychological state, nutritional status, and levels of social support (Pallis et al., 2010, Hurria and Cohen, 2016). A large-scale study across 10 hospitals which used CGA to screen 1967 patients with cancer aged ≥70 years found that unknown age-related problems were uncovered, which allowed for early intervention (25.7%) and changes in treatment decisions to benefit the patients (25.3%) (Kenis et al., 2012).

Methods

A comprehensive search strategy was developed, and four electronic databases (MEDLINE, EMBASE, The Cochrane Library, and Web Of Knowledge) were searched from January 2000 to May 2013 to systematically identify references for inclusion across the reviews. References were assessed for inclusion through two stages: two reviewers independently screened titles and abstracts for potentially relevant studies for each review (stage 1); full-text copies were obtained and independently assessed by two reviewers (stage 2). Disagreements were resolved by discussion with a third reviewer where necessary. Studies were excluded if they did not meet the inclusion criteria.

The reviews included evidence from randomised controlled trials (RCTs), subgroup analyses of RCT data, pooled analyses, cohort studies, and retrospective data. The included population was 'older' or 'elderly' people with lung cancer, NHL, colorectal cancer, breast cancer, CML and renal cell carcinoma. All forms of systemic anti-cancer therapy (including cytotoxic chemotherapy and biological agents) were considered and no restrictions were applied in terms of disease stage, tumour histology or the line of treatment across disease types.

Data on a wide range of variables were extracted into piloted data extraction forms (quality assessment, study design, patient characteristics, efficacy outcomes, QoL, and CGA) by one reviewer, and checked for accuracy by a second reviewer. Disagreements were resolved through discussion with a third reviewer where necessary. The included RCTs were assessed for methodological quality using criteria based on the Centre for Reviews and Dissemination guidance (Centre for Reviews and Dissemination (CRD), 2008) and the non-randomised studies were not quality assessed.

Findings

There were 490 studies included across the six individual reviews: breast cancer (n=74), colorectal cancer (n=85), lung cancer (n=199), renal cell carcinoma (n=9), CML (n=15), and NHL (n=108). Fully detailed methodology, results, and findings are available in the individual review reports, including information relating to contributions from clinical advisors and co-authors (Liverpool Reviews and Implementation Group, 2016).

There were very few studies across the six reviews which that explicitly reported the use of tools which the study authors had described as CGA. Information related to CGA use was reported in less than 10% (n=28) of studies overall, see Figure 1 for details. Individual study characteristics, details of the CGA tools used and how they were implemented are shown in Table 1.

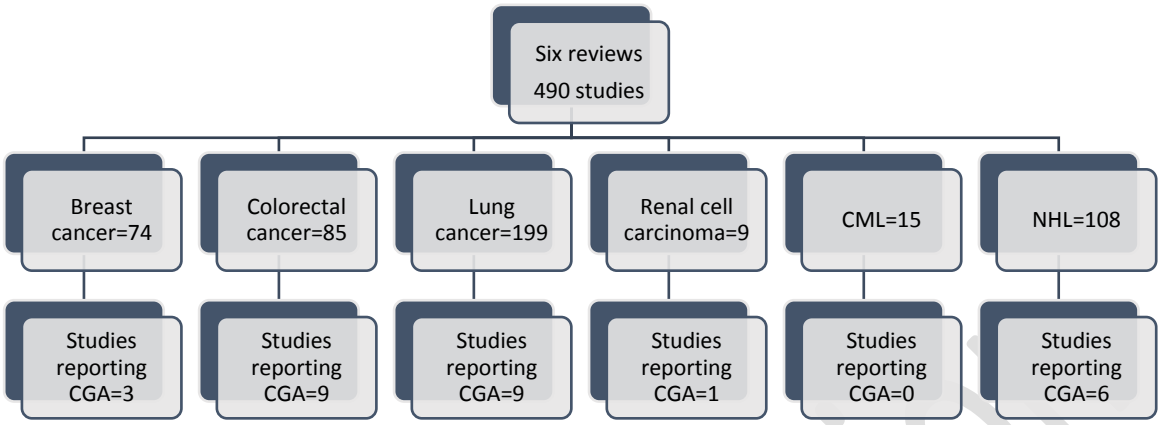

Figure 1 Number of studies reporting CGA

Table 1 Study characteristics and CGA tools used

	Study characteristics	Tool(s) used, how tool(s) used
Lung cancer		
LeCaer et al 2012	Phase II RCT France 2006-2010	CCI ADL IADL Used as eligibility criteria for patient selection
Biesma et al 2011	Phase III RCT Netherlands 2003-2006	CCI ADL IADL CIRS-G TUG MMSE GDS-15 PANAS GFI Baseline assessment and follow-up
LeCaer et al 2011	Phase II RCT France 2006-2008	CCI ADL IADL Used as eligibility criteria for patient selection
Gridelli et al 2003	Phase III RCT Italy 1997-2000	ADL IADL Baseline assessment and follow-up
Gridelli et al 2012	Phase I/II cohort study Italy 2000-2005	CCI ADL IADL Baseline assessment
Camerini et al 2010	Phase II cohort study Italy 2006-2009	BADL IADL Used as eligibility criteria for patient selection
LeCaer et al 2007	Phase II cohort study France 2003-2004	CCI Used as eligibility criteria for patient selection
LeCaer et al 2007	Phase II cohort study France 2003-2004	CCI Used as eligibility criteria for patient selection
Maestu et al 2007	Cohort study Spain 2001-2003	CCI IADL ADL Baseline assessment
NHL		
Merli et al 2012	RCT Italy 2003-2006	IADL Baseline assessment
Vitolo et al 2011	Cohort study Italy 2004-2007	Unspecified CGA Baseline assessment
Bernardi et al 2003 (abstract only)	Cohort study Italy 2000-2002	ADL IADL To categorise patients at enrolment in order to determine treatment regimen
Tucci et al 2009	Cohort study Italy 2003-2006	ADL CIRS-G To categorise patients into fit/unfit
Spina et al 2012	Phase II cohort study Italy	ADL IADL

	2000-2006	Geriatric depression MMSE CIRS-G As baseline measure and to categorise into fit/unfit
Taoka et al 2010	Cohort study Japan 2005-2009	ADL Baseline assessment and follow-up
Colorectal cancer		
Aparicio et al 2011 (abstract only)	Phase III RCT 2003-2010	CCI MMSE IADL GDS Baseline assessment
Sastre et al 2012	Phase III RCT subgroup 2002-2004	Independent Daily Activities Katz Scale Used as eligibility criteria for patient selection
Carreca et al 2011 (abstract only)	Cohort study 2009	Unspecified CGA Used as eligibility criteria for patient selection
Feliu et al 2006	Cohort study Japan 1999-2004	CCI, ADL and IADL Baseline assessment
Feliu et al 2005	Cohort study Spain 2002-2002	ADL Baseline assessment and follow-up
Mattioli et al 2005	Phase II cohort study Italy 2001-2004	ADL, IADL Baseline assessment and follow-up
Rosati et al 2005	Phase II cohort study Italy 2002-2004	ADL IADL Baseline assessment
Comella et al 2005	Phase II cohort study Italy 2001-2004	ADL, MMS, CCI Baseline assessment and follow-up
Daniele et al 2003	Cohort study Italy 1998-2000	ADL, IADL Baseline assessment
Breast cancer		
Romieu et al 2007	Phase II RCT France, Germany, Spain, UK, Switzerland 2002-2004	VES-13 Baseline assessment and follow-up
Nuzzo et al 2008	Phase III RCT Italy 2003-2006	IADL ADL Baseline assessment and follow-up
Hurria et al 2006	Cohort study USA 2001-2003	ADL, IADL, GDS, CCI, BMI Baseline assessment and follow-up
Renal cell carcinoma		
Brunello et al 2013	Retrospective review Italy 2006-2010	CIRS-G Used as baseline measure to stratify patients into fit/vulnerable/frail categories

FACT-L=Functional Assessment of Cancer Therapy for Lung Cancer; FACT-G=Functional Assessment of Cancer Therapy-General; LCSS=Lung Cancer Symptoms Scale; CCI=Charlson Comorbidity Index; ADL=Activities of daily Living; IADL=Instrumental Activities of Daily Living; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire; EORTC QLQ-LC13=EORTC Quality of Life Cancer Questionnaire – Lung Cancer. TOI=Trial Outcome Index; TOI-L=Trial Outcome Index-Lung; KPS=Karnofsky performance status; CIRS-G=Cumulative Illness Rating Scale for Geriatrics; TUG=Timed Up and Go test; MMSE=Mini-Mental State Examination; GDS=Geriatric Depression Scale; PANAS=Positive and Negative Affect Schedule; GFI=Groningen Frailty Indicator; PSI=Pulmonary Symptom Improvement; QoL=quality of life; PS=performance status; NR=not reported

As shown in Table 1, there were 11 different tools used for the purpose of CGA across the included studies, used either in combination or stand alone: Charlson Comorbidity Index (CCI), Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), Basic Activities of Daily Living (BADL), Cumulative Illness Rating Scale for Geriatrics (CIRS-G), Timed Up and Go Test (TUG), Mini-Mental State Examination (MMSE), Geriatric Depression Scale (GDS), Positive and Negative Affect Schedule (PANAS), Groningen Frailty Indicator (GFI), Vulnerable Elders Survey (VES-13), Independent Daily Activities Katz Scale.

Comprehensive geriatric assessment was implemented in a number of different ways across the included studies, as shown in Table 1. Eight studies used CGA as a baseline assessment measure in a similar way to disease stage or performance status (Daniele et al., 2003, Rosati et al., 2005, Feliu et al., 2006, Maestu et al., 2007, Aparicio et al., 2011, Vitolo et al., 2011, Gridelli et al., 2012, Merli et al., 2012). Nine studies used CGA to assess patients at baseline and at as follow-up different time points (Gridelli et al., 2003, Comella et al., 2005, Feliu et al., 2005, Mattioli et al., 2005, Hurria et al., 2006, Romieu et al., 2007, Nuzzo et al., 2008, Taoka et al., 2010, Biesma et al., 2011); seven studies used CGA tools as an assessment for eligibility in the study (LeCaer et al., 2007a, LeCaer et al., 2007b, Camerini et al., 2010, Carreca et al., 2011, LeCaer et al., 2011, LeCaer et al., 2012, Sastre et al., 2012); and four studies used CGA tools to categorise patients into subgroups for the purpose of data analysis (Bernardi et al., 2003, Tucci et al., 2009, Spina et al., 2012, Brunello et al., 2013).

Discussion

Overall, the reviews highlight a paucity of published data relating to the use of CGA tools in clinical study settings, which may be reflective of the lack of use in routine clinical practice. According to the clinicians advising the review team, the practicalities of conducting CGA assessment (usually by a clinical nurse specialist) are often considered time consuming and resource intensive and, as such, CGA is often not conducted in practice and is not routinely incorporated into the protocol for cancer study trials. Perhaps this is also in part due to the fact that gerontology and oncology have only (relatively) recently been linked in clinical practice (Birmingham, 2006). SIOG advocate the use of CGA in routine practice (International Society of Geriatric Oncology, 2016) as it enables clinicians to determine appropriate treatment choices for older people with cancer, which in turn leads to better outcomes in terms of benefit to the patients. It is therefore imperative that the routine use of CGA be incorporated into future research and is on the agenda for clinical nurse specialists.

The six reviews identified several CGA tools used in clinical studies, and with the exception of PANAS and BADL, the majority have been identified as commonly used CGA tools (Pallis et al., 2010, International Society of Geriatric Oncology, 2016). There are other commonly used CGA tools that are available to clinicians, which were not used in the included studies included in this review. For example: G8 Questionnaire, Mini Nutritional Assessment (MNA), Barthel Index, Senior Adult Oncology

Program, Adult Comorbidity Evaluation, MAX2 Index, 6-minute walk test, Short Portable Mental Status, and the Blessed Dementia Ratings Scale (Pallis et al., 2010, International Society of Geriatric Oncology, 2016).

All information relating to a patient's potential wellbeing and response to treatment is important when treatment decisions are being made as each individual's comorbidities and fitness need to be considered. How this information was collected and collated by investigators was often not adequately described in the studies included in the six reviews and, when presented, the reporting of CGA was poor and inconsistent. For example, it is not sufficient for study authors to specify which tools have been used, it is also useful for study authors to describe how, when and why CGA was undertaken.

Implications for future research

The general consensus of the clinical advisors who worked across the reviews is that the development and validation of specific CGA tools is required for use in UK clinical practice if a clearer picture of the eligibility of older people for treatment is to be communicated to the wider clinical community. This approach will also inform clinicians as to the specific experiences of older people receiving treatment for cancer. Perhaps the challenge is for nurses and clinical nurse specialists, who are at the front line of services for older people with cancer, to implement changes in routine practice. However, if routine use of CGA is time consuming and resource intensive, future research might need to focus on a streamlined and unified approach which balances resource use and patient benefit.

The reviews highlight that (chronological) age in itself should not be the only factor considered when choosing appropriate treatments for patients, therefore it is essential that reliable measures of fitness and comorbidity (characteristics of biological age) are developed and used consistently in both clinical trial settings and routine practice. The increased use of CGA in clinical practice could mean that a higher number of older patients are offered treatment, and an increase in the use of CGA in clinical studies could improve the numbers of older patients who are eligible for trials.

Conclusions

Findings from across the five reviews that included CGA-related information show that CGA is not routinely carried out in clinical trials and that the CGA data that are collected are limited. The incorporation of standardised CGA tools into the design of future clinical trials that include older patients will be key to the success of future research into the treatment of older people with cancer.

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