



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

## New horizons in systemic anti-cancer therapy in older people

**Citation for published version:**

Parry, JL, Hall, P & Young, J 2018, 'New horizons in systemic anti-cancer therapy in older people', *Age and Ageing*. <https://doi.org/10.1093/ageing/afy024>

**Digital Object Identifier (DOI):**

[10.1093/ageing/afy024](https://doi.org/10.1093/ageing/afy024)

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Peer reviewed version

**Published In:**

Age and Ageing

**Publisher Rights Statement:**

This is a pre-copyedited, author-produced version of an article accepted for publication in "Age and Ageing" following peer review. The version of record "New horizons in systemic anti-cancer therapy in older people" is available online at: <https://academic.oup.com/ageing/advance-article/doi/10.1093/ageing/afy024/4956946>

**General rights**

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

**Take down policy**

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact [openaccess@ed.ac.uk](mailto:openaccess@ed.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.



### New Horizons article for Age and Ageing

*“The area we would like you to focus on is new approaches to improving tolerability of chemotherapy in older people. Whilst a fair bit has been written on frailty assessment in patients with cancer ( which is an area geriatricians know a lot about) there has been much less exposure in the geriatric medicine literature on the topic of reducing toxicity and improving tolerability of therapies in older people. Some key areas I would be keen for the article to address would be issues around patient selection, benefits of newer agents with improved toxicity profiles, dose adjustment with age or fragility and the role of highly targeted therapies.”*

*~3000 words, 30-50 references.*

## **Systemic Anti-Cancer Therapy in the Elderly**

Parry JL,<sup>1</sup> Hall PS<sup>2</sup>, Young J<sup>3</sup>

**1. Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh EH4 2XR, UK.**

**2. Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh EH4 2XR, UK.**

**3. Bradford Institute for Health Research, Bradford Royal Infirmary, Bradford, BD9 6RJ, UK.**

### **Abstract**

Cancer is a disease associated with ageing. Increased life expectancy means that cancer in older adults is becoming an increasingly common problem. There are unique issues to consider when making decisions about cancer treatment in older populations. Unfortunately, however, this group is still under-represented in clinical trials for new cancer therapies meaning there are less evidence based data to guide management. This articles aims to look at how we can optimise cancer treatment for elderly patients with a focus on Systemic Anti-Cancer Therapy (SACT) and addressing particular issues around patient selection, improving treatment tolerance and use of newer agents with different toxicity profiles.

**Keywords- cancer, elderly, chemotherapy, targeted therapy, immunotherapy, toxicity, trials, systemic anti-cancer therapy**

### **Key points**

- With an ageing population there will be an increasing number of older patients living with, and undergoing treatment for, cancer.
- In recent years there has been a rapid expansion of the range of Systemic Anti-Cancer therapy (SACT) options available to the older population
- There are particular issues associated with the use of SACT in elderly patients
- There should be an initial comprehensive assessment to address which patients should be offered SACT and allow optimisation of patients' health prior to embarking upon it
- There should be ongoing attention to and, as far as possible, minimisation of SACT toxicity throughout and after treatment.
- Elderly patients are under –represented in clinical trials for SACT and we need to improve their recruitment levels.

## **Introduction**

With an ageing population and a continued increase in life expectancy, cancer in the older person has become an increasingly common problem in the Western world. More than three-quarters of cancer deaths occur in people aged 65 years and over, and more than half (52%) in those aged 75 years and over. (1)

Whilst the cancer burden is highest in the older age group, there is a growing body of evidence to suggest older patients are less likely to receive the most clinically effective treatment for their cancer. (2) (3) (4) Suboptimal treatment can lead to less favourable cancer outcomes and impact negatively on cancer survival rates. Concerns have been raised that current methods of assessing older patients do not provide sufficient information to make appropriate cancer treatment recommendations. Poorly managed co-morbidities, as well as lack of practical and social support, can also prevent patients receiving optimum treatment for their cancer.(5)

Cancer treatment can include surgery, radiotherapy and pharmacotherapy. This article focuses on specific issues related to the latter, reflecting on the use of Systemic Anti-Cancer Therapy (SACT) in older adults. It encompasses a summary of current SACTs available, including newer agents with different toxicity profiles, the existing evidence base and special considerations for the use of SACT in older people and provides suggestions of how cancer treatment might be improved for this population.

## **Systemic Anti-Cancer Therapy (SACT)**

SACT encompasses a host of pharmacological therapies that can be used with curative intent either *neoadjuvantly* with an aim to reduce the size or extent of the cancer before using radical treatment intervention or *adjuvantly* when given after the primary treatment to lower the cancer recurrence risk. They can also be used *palliatively* to prolong life or reduce symptoms.

SACT can be divided into four main categories:

**1) Chemotherapy which** encompasses traditional chemotoxic agents relying on the propensity of cells to die when their DNA is damaged by therapeutic means. Chemotherapies are not designed to specifically target malignant cells and therefore

many have a range of side effects that relate to their anti-proliferative actions such as alopecia, gastro-intestinal symptoms and myelosuppression. In addition, chemotherapy agents may have their own unique class specific side effects (Table 1).

**2) Hormonal (Endocrine) therapy** which deprives malignant cells of growth and survival promoting hormones. It is used for cancers derived from hormonally responsive tissues including breast, prostate and endometrium. It may work by inhibiting the production of hormones in their place of origin, inducing a chemical castration, or binding to the hormone receptor and preventing its activation. Potential side effects include increased risk of osteoporosis, metabolic syndrome, mood disorders, sexual dysfunction and impaired quality of life.

**3) Newer targeted agents** which work by interfering with specific molecules that are involved in the growth, progression and spread of cancer. They are frequently used in a sub-population who exhibit a specific molecular biomarker and may also be referred to as molecularly targeted therapies. They essentially target the underlying reason why the cells are multiplying out of control and are currently the focus of much anti-cancer drug development. Small molecule kinase inhibitors and monoclonal antibodies (mAbs) constitute the majority of these agents. Targets include;

-**extracellular growth factor receptors** such as Human Epidermal Growth Factor Receptor 2 (HER2). *Trastuzumab* is a monoclonal antibody directed against the extracellular segment of the HER2 receptor. The HER2 pathway promotes cell growth and division when it is functioning normally but when overexpressed cell growth accelerates beyond normal limits which can lead to rapid cell proliferation and tumour formation. The HER2 gene is amplified in 20-30% of early stage breast cancers and in patients with this overexpression of HER2, Trastuzumab can bind to the extracellular segment of the HER2 receptor preventing the growth factor receptor from working properly and inducing immune cells to kill that cell through antibody dependent cell mediated cytotoxicity.

- **intracellular signal transduction pathways**. Tyrosine kinases are enzymes that serve as intracellular messengers and help to send growth signals in the cell. *Tyrosine Kinase Inhibitors* (TKIs) are a class of agents that therefore interfere with signal transduction and can prevent cells growing and dividing. *Erlotinib* is a TKI that targets the epidermal growth factor receptor and has been shown to be effective in

the treatment of patients with metastatic non-small cell lung cancer.

- **angiogenesis.** Vascular Endothelial Growth Factor is a signal protein that stimulates new blood vessel formation. *Bevacizumab* is a monoclonal antibody that inhibits vascular endothelial growth factor. A blood supply is necessary for tumours to grow beyond a certain size so treatments that interfere with angiogenesis may block tumour growth.

**4) Immunotherapies** which can either stimulate the specific components of the immune system against the tumour cells or counteract signals produced by cancer cells that suppress immune responses. For example the immune checkpoint inhibitor *Ipilimumab*, used for the treatment of metastatic melanoma, is a monoclonal antibody which blocks the activity of a checkpoint protein CTLA- 4 which is expressed on the surface of activated T- lymphocytes. CTLA-4 serves to inactivate the T- cells and dampen the immune response and Ipilimumab therefore acts to prevent this inhibitory signal.

The expansion of newer targeted therapies and immunotherapies has been exponential in the last decade. These drugs require new approaches to optimise dosing, to assess patient adherence and to evaluate treatment effectiveness. In general they are tolerated better than traditional chemotherapy but are associated with their own range of adverse effects (Table 2). A review of the existing literature on the effects of targeted therapies in older people, has suggested that their early promise in terms of providing better tolerability has not yet been realised.(6)

## **Evidence for SACT in older people**

Despite the potential for more treatment complications, available data suggests that chemotherapy can be safe and effective in older patients (7) (8) (9). However, few studies to date have included patients at extremes of age, or with poor performance status and there are therefore less evidence-based data to guide the treatment of these patients (10) (11).

### **Trials**

#### **The Adjuvant Chemotherapy in elderly Women with breast cancer (ACheW)**

**study** (12) was an observational study that examined the patterns of treatment, and reasons for not offering treatment, in women with early breast cancer aged 70 years and over. Out of 803 patients referred to 24 multi-disciplinary cancer teams in England, only 116 (14%) were offered chemotherapy and 66 (8%) received it. Only 4 of 307 women (1.3%) aged over 80 years were offered chemotherapy. The most common reason for not offering chemotherapy was that 'other treatments were more appropriate' or 'benefits were too small'. Interestingly, co-morbidities and frailty were less commonly cited as reasons but there was evidence of inadequate assessment as in up to 1/3 of cases the recommendation for chemotherapy was made in the absence of critical information regarding performance status and HER-2 status. It was notable that patterns of treatment and reasons given for not offering chemotherapy showed considerable variation across hospital sites. This suggests that there is little consensus on the best management options for this older patient group.

The **UK National Cancer Research Network Adjuvant Chemotherapy in Older women (ACTION)** study (13) set out to address this issue in a randomised trial of adjuvant chemotherapy vs no chemotherapy in women aged over 70 years with early breast cancer. Unfortunately this study failed to recruit during the pilot phase, predominantly because the eligible older women who were approached were reluctant to participate in the study. The main conclusion was that a study that involved randomising older women to receive chemotherapy vs observation may not be a viable design for this patient population.

The **MRC FOCUS-2 trial** (Chemotherapy options in elderly and frail patients with metastatic colorectal cancer) (14) was a pivotal trial in selectively recruiting an elderly and frail population with advanced colorectal cancer who were previously untreated and considered unfit for full-dose chemotherapy. It showed that, even in this population, combination therapy with oxaliplatin and fluoropyrimidines was still preferable to single agent fluoropyrimidine. In FOCUS -2 the drug doses were started at 80% of standard doses, an adaptation commonly adopted outside trial practice. The moderate low rates of toxicity, along with low uptake of therapy escalation at six weeks seem to support this strategy. The 321GO and GO2 trials are now testing a similar approach in advanced gastric and oesophageal cancer.(15)

The **ELVIS study** (Elderly Lung cancer Vinorelbine Italian Study) was a randomized phase III trial in which patients older than 70 years affected by advanced Non Small Cell Lung cancer were randomized to receive best supportive care alone or best

supportive care plus chemotherapy with vinorelbine. The main end-point of the study was Quality of life and vinorelbine-treated patients scored better than control patients on Quality of life functioning scales, and also reported fewer lung cancer-related symptoms but did report worse toxicity-related symptoms.(16)

### National SACT dataset

The national collection of all systemic anti cancer treatment information in the NHS in England commenced in April 2012 and has allowed creation of a national SACT dataset. Similar data are available in Scotland. These data which relate to all cancer patients can be linked to information about patient demographics, co-morbidities and performance status as well as information about planned treatments, treatment modifications and intent of treatment. Analysis of these data also offers the potential to gain insight in to use of SACT amongst elderly patients.

### Designing trials

The FOCUS- 2 and GO2 trials represent a new approach to clinical design in elderly and frail patients. There should also be a more general move to try and discourage age being used as a specific exclusion criteria. There should be a greater emphasis on treatment outcomes analysis using routine registration of older people with cancer into large, comprehensive clinical data sets, though with careful attention to robust and standardised measures of co-morbidity, frailty and performance status.

New methods to measure treatment effects using routine data are also needed. It remains to be seen whether initiatives such as the SATURNE project (17), a project addressing whether chemotherapy is effective in patients with characteristics out-with the eligibility criteria of historical clinical trials, can provide reliable estimation.

### **Special considerations for Systemic Anti -Cancer Therapy in older people**

*Physiological factors-* The biology of certain cancers and their responsiveness to therapy changes with a patient's age. Furthermore, the physiological changes associated with aging may impact an older adult's ability to tolerate cancer therapy. Effects of renal function, hepatic metabolism and bone marrow reserve on the pharmacokinetic and pharmacodynamic properties of drugs can be considerable.

Older patients are more likely to have co-morbidities, be malnourished and have geriatric syndromes such as incontinence, falls, functional decline, polypharmacy and delirium. All of these factors can complicate dosing issues. Furthermore, if patients

have other disease states that are the dominant cause of poor quality of life and/or reduced life expectancy then treating the cancer may be inappropriate.

Detection of frailty is particularly important. A systematic review indicated that over half of older cancer patients have frailty or pre-frailty, and these patients are at considerably increased risk of mortality, post-operative complications and chemotherapy intolerance.(18)

*Psychosocial factors* - Poor practical and social support can also affect treatment tolerance. Older patients who live alone are less likely to accept treatment and access to transportation and available networks for home care also influence these decisions. (19) (20)

In patients with dementia there are specific treatment related issues. In most instances, individuals with mild dementia have decision-making capacity if the issues are explained to them and they are well supported. In individuals with more advanced dementias, carers and families might be asked to make proxy decisions. In some cases, the risks outweigh the benefits, for example, in patients with multiple comorbidities and high frailty where aggressive treatment might cause more distress. However, in individuals with mild dementia and longer life expectancies, the potential benefits could be significant and the person should not be denied them based on the 'dementia' label.

It should also not be forgotten that elderly patients might have a preference for a treatment potentially able to improve their quality of life rather than their survival. In a study of preferences for chemotherapy in patients with advanced non-small cell lung cancer, few (22%) patients reported they would choose chemotherapy for its likely survival benefit of 3 months but substantially more (68%) would choose it if it improved their quality of life.(21)

Optimal use of SACT in older patients requires characterisation of the functional reserve of an individual patient, both physically and mentally, along with assessment of the extent and severity of co-morbidities and their degree of social support. It should, therefore, involve careful decisions about which patients should be offered SACT (patient selection), attention to and as far as possible minimisation of SACT toxicity and, ideally, optimisation of patients' health prior to embarking upon SACT.

### *Patient Selection*

Due to the complex interplay between individual genetic and environmental factors we all experience ageing differently. Chronological age alone is a poor predictor of cancer treatment tolerance and efficacy(22). Work has therefore started to investigate risk prediction tools to help assess the individual risk of severe toxicity from chemotherapy developed specifically for use in older populations.

Extermann et al (23) developed the CRASH (Chemotherapy Risk Assessment Scale for High-Age Patients) score which stratifies patients aged over 70 years into four risk categories (low, medium-low, medium-high, and high) on the basis of both chemotherapy and patient variables. The four strongest predictors for haematological toxicity were Instrumental Activities of Daily Living score, lactate dehydrogenase level, diastolic blood pressure, and toxicity of the chemotherapy regimen. The four strongest predictors of non-haematological toxicity were Eastern Cooperative Oncology Group (ECOG) performance status (Table 3), Mini-Mental Status score, Mini-Nutritional Assessment score, and toxicity of the chemotherapy regimen.

Hurria et al (24) developed an alternative predictive model identifying patient age, (over 72 years) tumour type, receipt of standard dosing chemotherapy or polychemotherapy, anaemia & renal dysfunction, and reduced functional status (limited ability to walk one block, decreased social activities because of physical or emotional problems, falls in the last six months, and the need for assistance with taking medications) as risk factors for chemotherapy toxicity. In contrast they found that the commonly used Karnofsky Performance Status (KPS) (Table 3) did not identify older adults at increased risk for chemotherapy toxicity, highlighting the importance of developing risk stratification schema specifically for older adults.

## **SACT toxicities**

### **Measuring Toxicities**

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) is a descriptive terminology which can be utilized for describing and grading adverse events that occur during cancer therapy using drugs, biologics radiotherapy or surgery (25). They are also called "common toxicity criteria." Toxicity is graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4), with specific parameters according to the organ system involved. Death (Grade 5) is used for some of the criteria to denote a fatality. A category is a broad classification of Adverse Events based on anatomy and/or

pathophysiology. Within each CATEGORY, Adverse Events are listed accompanied by their descriptions of severity (Grade). Table 4 shows an example of grading from the blood disorders category.

### **Minimising SACT toxicities**

#### ***Chemotherapy toxicities***

*Cardiovascular toxicity* - Anthracyclines are associated with cardiac toxicity resulting in left ventricular dysfunction and congestive heart failure. Risk factors for anthracycline induced cardiotoxicity include co-morbidities such as hypertension, diabetes and coronary artery disease (all strongly age-related) and older age (a risk factor independent of comorbidities and performance status). The International Society of Geriatric Oncology (SIOG) have put forward proposals for the management of anthracyclines' cardiotoxicity risk including(26):

- rigorous screening to exclude patients at unacceptably high cardiac risk
- reduction in maximum cumulative dose
- measures to reduce cardiac toxicity (such as use of liposomal formulations, prolonged infusions or an iron chelating agent)
- regular monitoring of cardiac function and early management of dysfunction.

*Nephrotoxicity*- the age-related reduction in glomerular filtration rate (GFR) may lead to enhanced toxicity of drugs, particularly those with significant renal excretion, such as cisplatin, carboplatin, topotecan, methotrexate and ifosfamide. SIOG recommends that:

- renal function should be assessed at least by calculation of creatinine clearance in every patient even when serum creatinine is within the normal range, and doses adjusted according to degree of renal impairment
- where possible agents which are less likely to be influenced by renal clearance are used
- co-administration of known nephrotoxic drugs such as NSAIDS or Cox-2 inhibitors should be avoided or minimized.(27)

*Myelosuppression* – Older patients are at higher risk for severe and prolonged myelosuppression.:(28)(29)(30) Dose reductions and/or interruptions of chemotherapy regimens are necessary in patients with severe or life threatening

neutropenia, anaemia or thrombocytopenia. This can impact on outcome as well as contribute to a reluctance to administer chemotherapy in older patients, but there is some evidence that dose intensification, through dose interval reduction, facilitated by prophylactic granulocyte- colony stimulating factor (G-CSF) could improve survival in older cancer patients receiving chemotherapy.(31).

*Chemotherapy-induced nausea and vomiting (CINV)* can significantly affect a patient's quality of life and compliance with treatment. It can also put patients at risk of other complications such as acute kidney injury. Anti-emetic therapy with serotonin (5-HT<sub>3</sub>)-receptor antagonists, neurokinin-1-receptor antagonists, and corticosteroids can be extremely effective for the management of CINV. However older patients are susceptible to increased risk of anti-emetic side effects such as steroid- induced diabetes, constipation or QTc prolongation. Selection of appropriate anti-emetic therapy should therefore be on an individualised basis (32) (33).

*Fatigue* - In addition to treating the cancer and prolonging survival, a major goal of cancer therapy, especially in the elderly is the preservation of functional independence and quality of life. Such functional independence has been shown to be compromised by fatigue which has been a major complaint after administration of most traditional cytotoxic chemotherapy treatments. (34) (35). Pilot schemes in the UK have therefore started trialling the offer of practical or emotional support in the form of gardening, cooking, cleaning, transport or befriending to those patients over 70 embarking on Systemic Anti -Cancer Treatment.(5)

### ***Targeted therapy Toxicities***

It is widely believed that targeted agents provide effective and less toxic therapy while at the same time allowing patients to maintain their functional independence. Their use in the elderly patients has therefore been embraced with great hope and growing interest. Nonetheless these agents are still associated with some unique and potentially severe toxicities which can be more pronounced in the older age group. For example;

*Trastuzumab* - greater risk of congestive heart failure and left ventricular dysfunction

*Erlotinib* - greater rash, stomatitis, dehydration, anorexia and fatigue

*Bevacizumab* – greater drug induced hypertension & number of arterial thrombo-embolic events.

### ***Immunotherapy Toxicities***

The immunotherapies have the potential to precipitate a wide range of inflammatory adverse reactions resulting from increased or excessive immune activity. These immune-related reactions may include pneumonitis, hepatitis, colitis, nephritis, endocrinopathies and rash. They can be life-threatening and appear during the treatment course, or after the treatment has completed.

Awareness of the potential for these toxicities and prompt intervention according to specific guidelines (usually available from local oncology services) can prevent the toxicities escalating.

### ***Endocrine Therapy Toxicities***

In patients receiving endocrine therapy physicians need to be vigilant about optimising bone, cardiovascular and mental health. Clear guidelines providing suggestions of how to best manage these treatment complications such as use of appropriate anti-depressants for mood disorders (some are recognised to interact with endocrine therapy) and use of appropriate screening and relevant interventions to maintain bone and cardiovascular health need to be developed in conjunction with relevant specialists and made available to generalists.

### ***Optimising SACT in older patients- a new approach***

Strategies to optimise tolerance of SACT in older patients have hitherto involved adapted treatment regimens (dose reduction, selection of particular agents according to side effect profile), use of prophylactic G-CSF or rigorous screening to exclude patients at unacceptably high risk. More recently there has been a growing recognition of the importance of optimizing the physical and psycho- social health of older patients prior to receiving SACT. This involves identification of physical and psychosocial needs and the International Society of Geriatric Oncology (SIOG) recommends the use of Comprehensive Geriatric Assessment (CGA) prior to medical or surgical intervention for older cancer patients. This encompasses a review of frailty, co –morbidity, geriatric syndromes (eg falls, incontinence), mental health, functional difficulties and social circumstances. Rather than using this assessment to risk stratify patients, it is being adopted as a clinical process for treatment optimisation.

Kalsi et al (36) recently carried out a study to evaluate the impact on chemotherapy toxicity and tolerance of geriatrician delivered clinical interventions for co-existing needs as identified by a CGA for older (>70yrs) patients with cancer. The non-randomised study involved 135 patients (70 control, 65 intervention) undergoing chemotherapy in a London hospital. The observational group received standard oncology care. The intervention group underwent risk stratification using a patient completed screening questionnaire and high risk patients received CGA. The intervention participants undergoing CGA each received a mean of 6 intervention plans. These patients were more likely to complete cancer treatment as planned and fewer required treatment modifications. Kalsi et al have therefore proposed that standard oncology care should shift to a more pro-active model of medically optimising elderly patients for SACT, a concept referred to as prehabilitation. (37)

## **Changing mindsets**

Clearly, to offer aggressive treatment is not always clinically appropriate and overtreatment is just as undesirable as undertreatment. However advanced age alone should not be an exclusion criteria for the use of effective cancer treatment that could improve quality of life or extend meaningful survival and it is evident that there is much work to be done to ensure that we are not failing older patients. The recent UK Department of Health's 'Cancer services Coming of Age report' (5) has set out key principles for the development of an 'age friendly cancer service.' (Box1).

The Independent Cancer Taskforce has also specifically recognised the needs of older people in their recently published National Cancer Strategy, proposing recommendations outlined below (Box 2) (38).

## **Conclusion**

With an ageing population, a rapid expansion of the range of systemic anti-cancer therapy options available and the increasing chronic nature of cancer management, it is inevitable that there will be an expanding number of elderly patients living with, and undergoing treatment for, cancer. These patients will require medical professionals who are equipped to help them decide the best treatment course for their cancer, to ensure that they are in the optimum condition to receive it and to help them manage potential ongoing complications of their disease or its treatment. In

order to do this we need to improve the evidence base for the use of systemic anti-cancer treatments in older patients by increasing recruitment of older patients to clinical trials. We also need to work on improving links between elderly care specialists and oncologists to ensure we provide a cancer service that is tailored to meet the specific, and often complex, physiological and psycho-social needs of this growing cohort of patients.

## **References**

1. Cancer mortality by age | Cancer Research UK [Internet]. Available from: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/age#heading-Zero>
2. Hurria A, Wong F, Villaluna D, Bhatia S. Role of age and health in treatment recommendations for older adults with breast cancer: the perspective of oncologists and primary care providers. *J Clin Oncol* [Internet]. 2008 [cited 2016 Nov 14]; Available from: <http://jco.ascopubs.org/content/26/33/5386.short>
3. Gupta S, Lamont E. Patterns of presentation, diagnosis, and treatment in older patients with colon cancer and comorbid dementia. *Am Geriatr Soc* [Internet]. 2004 [cited 2016 Nov 14]; Available from: <http://onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2004.52461.x/full>
4. Berry M, Worni M, Pietrobon R, D'Amico T. Variability in the treatment of elderly patients with stage IIIA (N2) non-small-cell lung cancer. *J Thorac Oncol* [Internet]. 2013 [cited 2016 Nov 14]; Available from: <http://www.sciencedirect.com/science/article/pii/S1556086415328495>
5. Cancer Services Coming of Age: Learning from the Improving Cancer Treatment Assessment and Support for Older People Project. 2012;
6. Gonsalves W, Ganti AK, Jemal A, Siegel R, Ward E, et al. Targeted anti-cancer therapy in the elderly. *Crit Rev Oncol Hematol* [Internet]. 2011 Jun [cited 2016 Nov 14];78(3):227–42. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20599391>
7. Chen H, Cantor A, Meyer J, Corcoran MB, Grendys E, Cavanaugh D, et al. Can older cancer patients tolerate chemotherapy? A prospective pilot study. *Cancer*. 2003;97(4):1107–14.
8. Sargent DJ, Goldberg RM, Jacobson SD, Macdonald JS, Labianca R, Haller DG, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *N Engl J Med* [Internet]. 2001;345(15):1091–7. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11596588](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11596588)
9. Hung A, Mullins CD. Relative effectiveness and safety of chemotherapy in elderly and nonelderly patients with stage III colon cancer: a systematic review. *Oncologist* [Internet]. 2013 [cited 2016 Nov 14];18(1):54–63. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23299774>
10. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Albain KS. Underrepresentation of Patients 65 Years of Age or Older in Cancer-Treatment Trials. *N Engl J Med* [Internet]. 1999 Dec 30 [cited 2018 Jan 10];341(27):2061–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10615079>
11. Hurria A, Levit LA, Dale W, Mohile SG, Muss HB, Fehrenbacher L, et al. Improving the Evidence Base for Treating Older Adults With Cancer: American Society of Clinical Oncology Statement. *J Clin Oncol* [Internet]. 2015 Nov 10 [cited 2016 Aug 4];33(32):3826–33. Available from: <http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.63.0319>
12. Ring A, Harder H, Langridge C, Ballinger RS, Fallowfield LJ. Adjuvant chemotherapy in elderly women with breast cancer (AChEW): an observational study identifying MDT perceptions and barriers to decision making. *Ann Oncol* [Internet]. 2013 May [cited 2016 Aug 12];24(5):1211–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23334117>
13. Leonard R, Ballinger R, Cameron D, Ellis P, Fallowfield L, Gosney M, et al. Adjuvant chemotherapy in older women (ACTION) study – what did we learn from the pilot phase? *Br J Cancer*. 2011;105:1260–6.
14. Seymour MT, Thompson LC, Wasan HS, Middleton G, Brewster AE, Shepherd SF, et al. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. *Lancet*. 2011;377(9779):1749–59.
15. Hall PS, Lord SR, Collinson M, Marshall H, Jones M, Lowe C, et al. A randomised phase II trial and feasibility study of palliative chemotherapy in frail or elderly patients with advanced gastroesophageal cancer (321GO). *Br J Cancer* [Internet]. 2017 Feb 17 [cited 2018 Jan 27];116(4):472–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28095397>
16. Di Maio M, Perrone F. Quality of Life in elderly patients with cancer. *Health Qual Life Outcomes* [Internet]. 2003 Sep 17 [cited 2018 Jan 10];1:44. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14525617>
17. SATURNE | The University of Edinburgh [Internet]. [cited 2018 Jan 27]. Available from: <https://www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies/health-economics-studies/saturne>
18. Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol* [Internet]. 2015 Jun 1 [cited 2018 Jan 9];26(6):1091–101. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25403592>
19. Shariat SF, Milowsky M, Droller MJ. Bladder cancer in the elderly. *Urol Oncol* [Internet]. 2009 [cited 2016 Aug 23];27(6):653–67. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19879476>
20. Cavalli-Björkman N, Qvortrup C, Sebjørnsen S, Pfeiffer P, Wentzel-Larsen T, Glimelius B, et al. Lower treatment intensity and poorer survival in metastatic colorectal cancer patients who live alone. *Br J Cancer* [Internet]. 2012 Jun 26 [cited 2016 Aug 23];107(1):189–94. Available from: <http://www.nature.com/doi/10.1038/bjc.2012.186>
21. Silvestri G, Pritchard R, Welch HG. Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. *BMJ* [Internet]. 1998 Sep 19 [cited 2018 Jan 10];317(7161):771–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9740561>
22. Gillespie TW, Patterson H, Harris WB, Shumate M, Nadella P, Jacobs J, et al. Improving clinical outcomes in elderly oncology patients. *ASCO Meet Abstr*. 2004;22(14\_suppl):6075.
23. Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, et al. Predicting the Risk of Chemotherapy Toxicity in Older Patients: The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) Score.
24. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: A prospective multicenter study. *J Clin Oncol*. 2011;29(25):3457–65.
25. Cancer Institute N. Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events v4.0 (CTCAE). 2009 [cited 2018 Jan 9]; Available from: [https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_5x7.pdf](https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)
26. Aapro M, Bernard-Marty C, Brain EGC, Batist G, Erdkamp F, Krzemieniecki K, et al. Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper. *Ann Oncol* [Internet]. 2011 Feb 1 [cited 2016 Aug 23];22(2):257–67. Available from:

- <http://annonc.oxfordjournals.org/cgi/doi/10.1093/annonc/mdq609>
27. Launay-Vacher V. Cancer and the kidney: individualizing dosage according to renal function. *Ann Oncol* [Internet]. 2013 Nov 1 [cited 2016 Aug 23];24(11):2713–4. Available from: <http://annonc.oxfordjournals.org/cgi/doi/10.1093/annonc/mdt431>
  28. Begg CB, Carbone PP. Clinical trials and drug toxicity in the elderly. The experience of the Eastern Cooperative Oncology Group. *Cancer* [Internet]. 1983 Dec 1 [cited 2016 Aug 23];52(11):1986–92. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/6354419>
  29. Balducci L, Repetto L. Increased risk of myelotoxicity in elderly patients with non-Hodgkin lymphoma. *Cancer* [Internet]. 2004 Jan 1 [cited 2016 Aug 23];100(1):6–11. Available from: <http://doi.wiley.com/10.1002/cncr.11861>
  30. Langer CJ, Manola J, Bernardo P, Kugler JW, Bonomi P, Cella D, et al. Cisplatin-Based Therapy for Elderly Patients With Advanced Non-Small-Cell Lung Cancer: Implications of Eastern Cooperative Oncology Group 5592, a Randomized Trial. *CancerSpectrum Knowl Environ* [Internet]. 2002 Feb 6 [cited 2016 Aug 23];94(3):173–81. Available from: <http://jnci.oxfordjournals.org/cgi/doi/10.1093/jnci/94.3.173>
  31. Repetto L, Biganzoli L, Koehne CH, Luebke AS, Soubeyran P, Tjan-Heijnen VCG, et al. EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer. *Eur J Cancer* [Internet]. 2003 Nov [cited 2016 Aug 23];39(16):2264–72. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14556916>
  32. Aapro M, Johnson J. Chemotherapy-induced emesis in elderly cancer patients: the role of 5-HT3-receptor antagonists in the first 24 hours. *Gerontology* [Internet]. [cited 2016 Aug 23];51(5):287–96. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16110229>
  33. Jakobsen JN, Herrstedt J. Prevention of chemotherapy-induced nausea and vomiting in elderly cancer patients. *Crit Rev Oncol Hematol* [Internet]. 2009 Sep [cited 2016 Aug 23];71(3):214–21. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19162507>
  34. Karakoç T, Yurtsever S. Relationship between social support and fatigue in geriatric patients receiving outpatient chemotherapy. *Eur J Oncol Nurs* [Internet]. 2010 Feb [cited 2016 Nov 14];14(1):61–7. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S1462388909000854>
  35. Luciani A, Jacobsen PB, Extermann M, Foa P, Marussi D, Overcash JA, et al. Fatigue and Functional Dependence in Older Cancer Patients. *Am J Clin Oncol* [Internet]. 2008 Oct [cited 2016 Nov 14];31(5):424–30. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000421-200810000-00004>
  36. Kalsi T, Babic-Illman G, Ross PJ, Maisey NR, Hughes S, Fields P, et al. The impact of comprehensive geriatric assessment interventions on tolerance to chemotherapy in older people. *Br J Cancer*. 2015;112.
  37. Silver JK, Baima J. Cancer Prehabilitation. *Am J Phys Med Rehabil* [Internet]. 2013 Aug [cited 2018 Jan 9];92(8):715–27. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23756434>
  38. ACHIEVING WORLD-CLASS CANCER OUTCOMES. 2015 [cited 2018 Jan 9]; Available from: [https://www.cancerresearchuk.org/sites/default/files/achieving\\_world-class\\_cancer\\_outcomes\\_-\\_a\\_strategy\\_for\\_england\\_2015-2020.pdf](https://www.cancerresearchuk.org/sites/default/files/achieving_world-class_cancer_outcomes_-_a_strategy_for_england_2015-2020.pdf)

Appendix

**Table 2**  
**Examples of adverse effects associated with targeted anti-cancer therapy and immunotherapy**

Therapy	Target	Tumour type used to treat	Potential adverse side effects
<b>Bevacizumab</b>	Vascular endothelial growth factor (VEGF)	Colorectal, ovarian	Gastrointestinal perforation, wound healing complications, haemorrhage, arterial and venous thrombo-embolism, proteinuria, hypertension, reversible posterior leucoencephalopathy syndrome (RLPS)
<b>Trastuzumab</b>	Human epidermal growth factor receptor 2 (HER2)	Breast	Cardiomyopathy, especially if co-administered with anthracycline chemotherapy, infusion related reaction
<b>Erlotinib</b>	Epidermal growth factor receptor (EGFR) tyrosine kinase	Lung	Acneiform rash, diarrhoea, nausea and vomiting, elevated liver enzymes, pneumonitis
<b>Sunitinib</b>	Multiple receptor tyrosine kinases	Renal	Fatigue, skin discolouration, haemorrhage, stomatitis, nausea&vomiting, hypertension, hypothyroidism, osteonecrosis of the jaw
<b>Ipilimumab</b> □	Cytotoxic T-lymphocyte associated antigen 4 (CTLA-4)	Melanoma	Fatigue, rash, colitis, hepatitis, hypophysitis, hypo/hyperthyroidism, hypopituitarism
<b>Pembrolizumab</b> □	Programmed cell death 1 (PD-1) immune checkpoint inhibitor	Melanoma, lung	Fatigue, rash, colitis, hepatitis, hypo/hyperthyroidism, arthralgia, myalgia, pneumonitis

□immunotherapy

**Table1**  
**Examples of adverse effects associated with traditional chemotherapeutic agents**

<b>Chemotherapy Class</b>	<b>Example</b>	<b>Tumour type used to treat</b>	<b>Potential Adverse Side Effects in addition to fatigue, myelosuppression, nausea &amp; vomiting</b>
<b>Alkylating agents</b>	Cisplatin, carboplatin, cyclophosphamide	Lung, ovarian , testicular, breast	Nephrotoxicity, ototoxicity, thromboembolic events
<b>Anthracyclines</b>	Epirubicin, doxorubicin	Breast, sarcoma	Alopecia, cardiotoxicity, secondary malignancies
<b>Taxanes</b>	Paclitaxel, docetaxel	Ovarian, breast , lung	Alopecia, peripheral neuropathy, arthralgia, hypersensitivity reaction, diarrhoea
<b>Vinca alkaloids</b>	Vincristine, vinorelbine	Breast, lung	Headache, constipation, peripheral neuropathy
<b>Anti- metabolites</b>	Methotrexate, 5 – fluorouracil, capecitabine, gemcitabine	Colorectal, oesophageal, lung	Hand- foot syndrome, cardiotoxicity, nephrotoxicity

<b>ECOG PERFORMANCE STATUS</b>	<b>KARNOFSKY PERFORMANCE STATUS</b>
<b>0—Fully active, able to carry on all pre-disease performance without restriction</b>	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
<b>1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</b>	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
<b>2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours</b>	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
<b>3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours</b>	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
<b>4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair</b>	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
<b>5—Dead</b>	0—Dead

**Table 3**  
**Table comparing the Eastern Cooperative Oncology Group (ECOG) Performance Status to the Karnofsky Performance Status (KPS)**

**Table 4****Adapted from National Cancer Institute Common Terminology Criteria for Haematological Toxicity**

Blood element	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)	Grade 5
Neutrophils	<reference range to 1.5 x 10 <sup>9</sup> /L	1 to 1.5 x 10 <sup>9</sup> /L	0.5 to 1 x 10 <sup>9</sup> /L	<0.5 x 10 <sup>9</sup> /L	
Platelets	<reference range to 75 x10 <sup>9</sup> /L	50 to75 x 10 <sup>9</sup> /L	25 to 50 x 10 <sup>9</sup> /L	<25 x 10 <sup>9</sup> /L	
Haemoglobin	<reference range to 100g/L	80 to 100g/L	<80g/L	Life-threatening consequences; urgent intervention indicated	Death

**Box 1 - Key principles for the development of an age friendly cancer service from CANCER SERVICES COMING OF AGE , a report from the Department of Health.**

- *Engaging elderly care specialists as an active part of the cancer care team.*
- *Adoption of a multidisciplinary approach to the assessment and management of all patients.*
- *Ensuring an early and appropriate assessment of an older person to identify and address unmet physical, psychological and social support needs prior to embarking on cancer treatment with further follow up assessments to be undertaken at defined points throughout the treatment journey, to identify and address changes in need.*
- *Effective management of other health conditions and incorporating reasonable adjustments into care planning to address additional needs.*
- *Establishment of services and clear referral pathways to address needs identified by assessment. This includes establishing clear links with voluntary sector agencies, social services, and specialist teams such as falls prevention teams, continence specialists and dementia specialists.*

**Box 2- Recommendations for achieving world class cancer outcomes in older people from ACHIEVING WORLD-CLASS CANCER OUTCOMES A STRATEGY FOR ENGLAND 2015-2020, a report from the independent Cancer Taskforce.**

- **Recommendation 41:** *NHS England, the Trust Development Authority and Monitor should pilot a comprehensive care pathway for older patients (aged 75 and over in the first instance). This pathway should incorporate an initial electronic health needs assessment, followed by a frailty assessment, and then a more comprehensive geriatric needs assessment if appropriate. The pilot should evaluate a model in which the outputs of these assessments are considered by the MDT in the presence of a geriatrician, who would advise on Allied Health Professional needs, co-morbidities etc, and their implications for treatment and emotional and physical support.*
- **Recommendation 42:** *NHS England should ask the National Institute for Health Research and research charities to develop research protocols which enable a better understanding of how outcomes for older people could be improved.*